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STUDIES IN MONGOLISM

III. THE PITUITARY BODY

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In the previous paper dealing with the role of the thyroid in mongolism, I pointed out that involutional changes were observed in all my cases. One may distinguish between the histologic structure of the thyroid of mongoloid children in the first two years of life and that of mongoloid children after the first six years. In the former group irregular parenchymatous growth without formation of vesicles and a number of greatly enlarged tubules and marked increase of connective tissue prevail; in the latter group distention of vesicles with colloid and invasion of colloid in the intertubular spaces are conspicuous, while the thyroid as a whole is small and underdeveloped. I pointed out that there may be premature stimulation of the thyroid, even hyperthyroidism, during fetal life, but after birth one finds only involutional changes and hyperactivity appears to be replaced by degenerative processes. Such a picture is suggestive of a disorder of the pituitary rather than a primary disease of the thyroid.

In this article I shall present the results of investigations on the pituitary body in 14 cases. In 13 instances the diagnosis of mongolism was without question; in 1 the diagnosis was first considered but was later discarded.

METHODS

The material consisted of 6 cases of mongolism in children observed at the Wrentham State School. The children died of intercurrent diseases, and I performed autopsies. A study of all the endocrine glands was carried out. Observations were made and autopsies done on 7 patients at the Children's Hospital, Boston. By permission of Dr. Sidney Farber, I have been able to study material from these patients. One patient was observed in the Walter E. Fernald State School. Through Dr. Paul Yakovlev, I had the opportunity to attend the autopsy and received material for further examination.

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The material from the Children's Hospital was fixed in formaldehyde; some was fixed in Zenker's or Bouin's fluid or in formaldehyde. Of late, I have adopted a fixative which consists of a mixture of potassium bichromate, acetic acid and formaldehyde. This fixative is, in my opinion, superior to those which were used before. The material was embedded in paraffin and cut in sections from 5 to 8 microns in thickness. Material in all cases was stained with the Mallory triple stain to obtain uniform results which would facilitate comparison of observations in the various cases and those in cases studied by other investigators. Besides this method, those of Dominici, Mann, Collin and Heidenhain and the hematoxylin and eosin stain were used. Recently, I have also used the method of Masson and Severinghaus, which surpasses all former methods in clearness and constancy. From Dr. MacCallum I learned Poirrier's blue-eosin stain, which gives excellent results after fixation in Zenker's fluid and is of special value for demonstration of the beta granules. With formaldehyde-fixed material the results were far less satisfactory.

A more extensive discussion of the technic and the cases used as controls will be given in another paper, which deals with the pituitary body in various diseases of infancy.

REPORT OF OBSERVATIONS

CASE 1.—*Two day old mongoloid girl.*

In horizontal sections the anterior and posterior lobes were seen. The latter did not appear noteworthy. The glandular tissue of the anterior lobe corresponded in amount to that of a normal gland of a child of the same age. The eosinophils were conspicuous, their size and number apparently being normal. Except for the eosinophils, the amount of degeneration in the parenchyma was obvious. Most of the cells had pyknotic nuclei, the chromatin of which was dark blue or red. The elements of the protoplasmic syncytium were conglomerated and clustered and stained violet. No basophils were recognizable. If the eosinophils were degenerated to the same degree as were the other cells, it would have been impossible to decide whether or not the degeneration was artificial. The patchy degeneration, however, seems to indicate that the pathologic changes in the chromophobic and basophilic cells were significant.

CASE 2.—*Six week old mongoloid girl.*

On horizontal section only the anterior lobe was seen. The pituitary body appeared small. The frontal diameter was approximately 5 mm. The whole lobe appeared uniform. With the Mallory stain most of the cells had reddish, degenerated nuclei. With the Dominici stain the nuclei appeared dark blue, owing to the coarse chromatin structure of the nuclei. Within this uniform picture there were about ten fields in which basophilic cells with a larger amount of protoplasm were to be recognized. These cells had dark blue-violet protoplasmic bodies, and the nuclei were either transparent with dark blue chromatin or wholly degenerated and red. Except for this small area, the lobe was composed of degenerated cells which had no visible protoplasm. When protoplasm was visible, it was reddish violet, irregular and without recognizable boundaries.

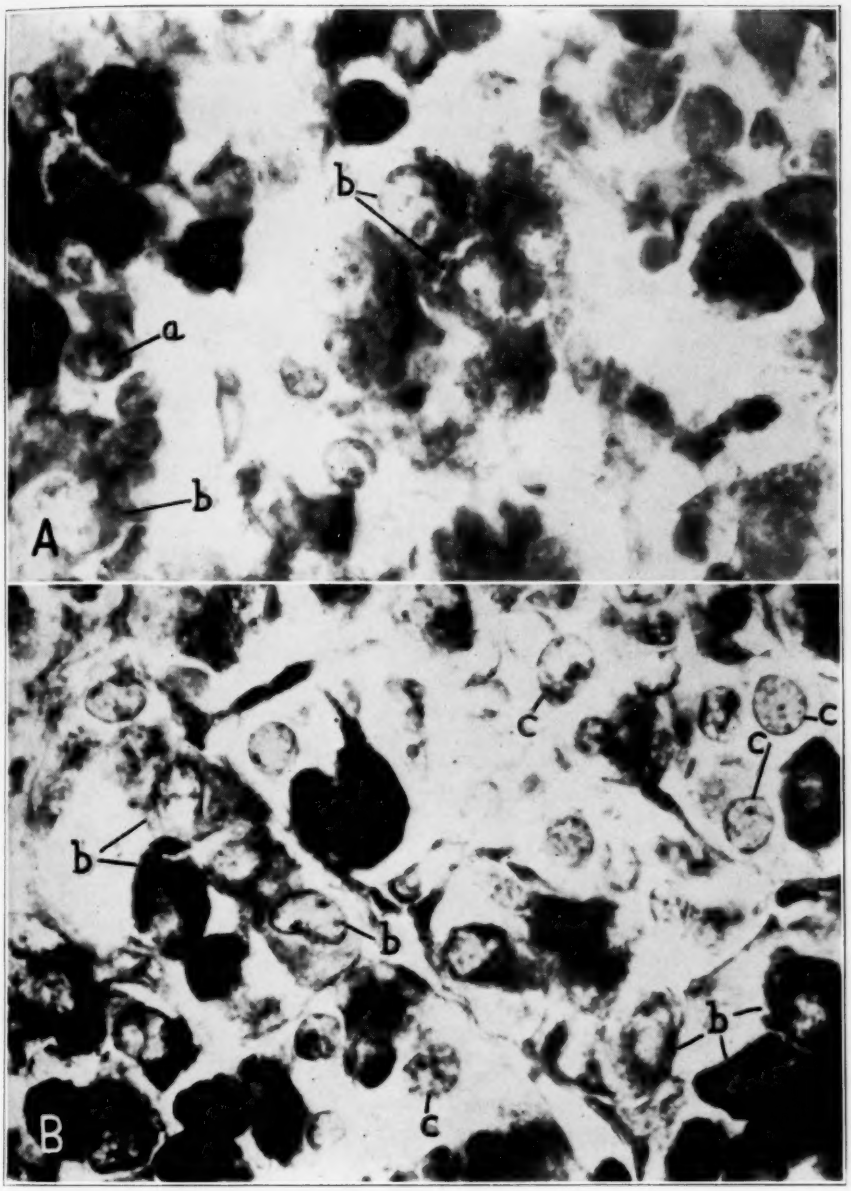

Fig. 1.—Normal cells of the anterior lobe of the pituitary body in children. Magnification, × 750.

A shows the normal gland of a 3 month old girl. *a* indicates acidophils, with nuclei from 9 to 10 microns in diameter, and *b*, basophils, with nuclei about 16.5 microns in diameter. The basophils show different stages of beta granulation. *B* shows the gland of a 2 month old prematurely born girl (case 3). Notice the remarkable development of basophils in different stages of granulation. Here, *C* indicates chromophobic cells.

As a whole, examination of the gland in this case revealed that there was no definite differentiation into the three types of cells or formation of definite glandular structure. The cells were densely piled, and, except for definitely mature basophils, the whole anterior lobe was composed of embryonic parenchyma without differentiation (fig. 2 *A*).

CASE 3.—*Prematurely born 2 month old girl.*

The lobe, seen under a low power lens, formed a field of scattered bright red cells and many chromophobic cells. Both cell types were present in nearly the same numbers. Some basophilic cells were recognizable among the chromophobic elements. Cytologic analysis with the highest magnification revealed in the middle field well preserved cells. Many degenerated nuclei were visible, but as a whole the gland seemed in good condition. The eosinophilic cells had bright red protoplasm. The nuclei were round and transparent, with some chromatin and a bright red nucleolus. Special interest was placed in the chief cells and basophils. The chief cells were numerous in many fields. They were large and transparent, usually with two bright red nucleoli. Only a few basophilic cells were present, but these showed large nuclei surrounded by bluish gray protoplasm. They were growing basophils, without degenerated nuclei; they did not have the dark blue protoplasm seen in the adult gland. Figure 1 *B* shows a field with growing basophilic cells. They are in different stages of development, from cells with large nuclei and slight, faint blue protoplasm to large cells with darker blue reaction. Comparison of the large nuclei of these cells and the small nuclei of the eosinophilic cells shows clearly the difference between the two types. As a whole, the gland appeared normal (fig. 1 *B*).

CASE 4.—*Three month old mongoloid boy.*

The anterior and the posterior lobe, separated by the cleft, were observed in horizontal sections. The posterior lobe was lined, in the region of the cleft, with many layers of epithelium. Many small and large "cysts," without content, were recognizable. The strands of connective tissue were dense, while the glia formed a fine network. No other types of cells were seen.

The anterior lobe appeared similar to that in case 2. The gland consisted of small nucleated cells without much protoplasm. The nuclei varied in shape, some being round and others oval, and the slight protoplasm was a faint grayish blue. It may be best to rank cells of this type as embryonic chief cells. These cells are not similar to the mature forms. They are small, undifferentiated cells with dark chromatin structure. No development into eosinophils or basophils could be recognized. The cells did not form a glandular structure; they were suspended in a meshwork of connective tissue, resembling grapes. Many spaces separated the cells, and frequently red blood cells could be seen within the spaces (fig. 2 *B*).

CASE 5.—*Five month old mongoloid boy.*

The pituitary body was very small, weighing 0.085 Gm.; the frontal diameter was 6 mm., and the sagittal diameter 5 mm. In sections the anterior and posterior lobes were seen, but the posterior lobe was small and incomplete. No definite statement is possible as to whether its structure was normal.

In the anterior lobe the number of eosinophilic cells was so increased that under a low power lens the lobe seemed to consist almost entirely of eosinophilic cells. They were enlarged, with small nuclei, and formed tubules. The nuclei were blue, round and rich in chromatin, but many were bright red, which increased the red appearance of the sections. With a high power lens, some chromophobic cells

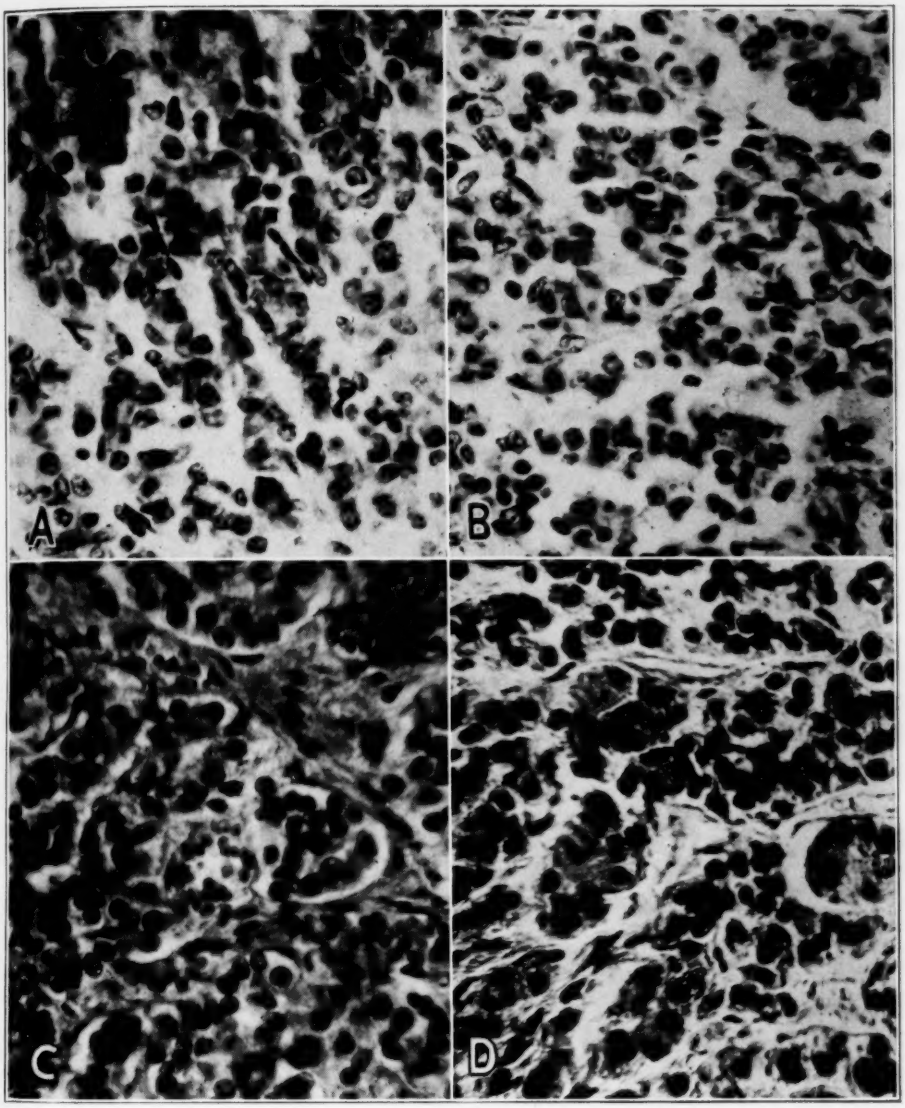

Fig. 2.—Cells of the anterior lobe of the pituitary of persons with mongolism. Magnification, × 400.

A is from a 6 week old mongoloid girl (case 2); *B*, from a 3 month old mongoloid boy (case 4); *C*, from a 13 month old mongoloid boy (case 9), and *D*, from a 30 year old mongoloid man (case 14). In the first 2 cases the anterior lobe was entirely composed of embryonic chromophobic cells, without differentiation into basophilic and acidophilic cells. In the other 2 cases the anterior lobe contained almost exclusively eosinophils. Notice the arrangement of cells in small strands in *D* (case 14).

could be recognized. The nuclei were small and round, with blue chromatin. They resembled the nuclei of eosinophilic cells. A few cells were seen with violet-blue protoplasm and completely degenerated nuclei.

The histologic picture in this case was characterized by prevalence of eosinophilic cells, which composed the whole anterior lobe. There was complete absence of the large fields of chromophobic cells that are normally seen at this age. Basophilic cells were not recognized (fig. 3 *A*).

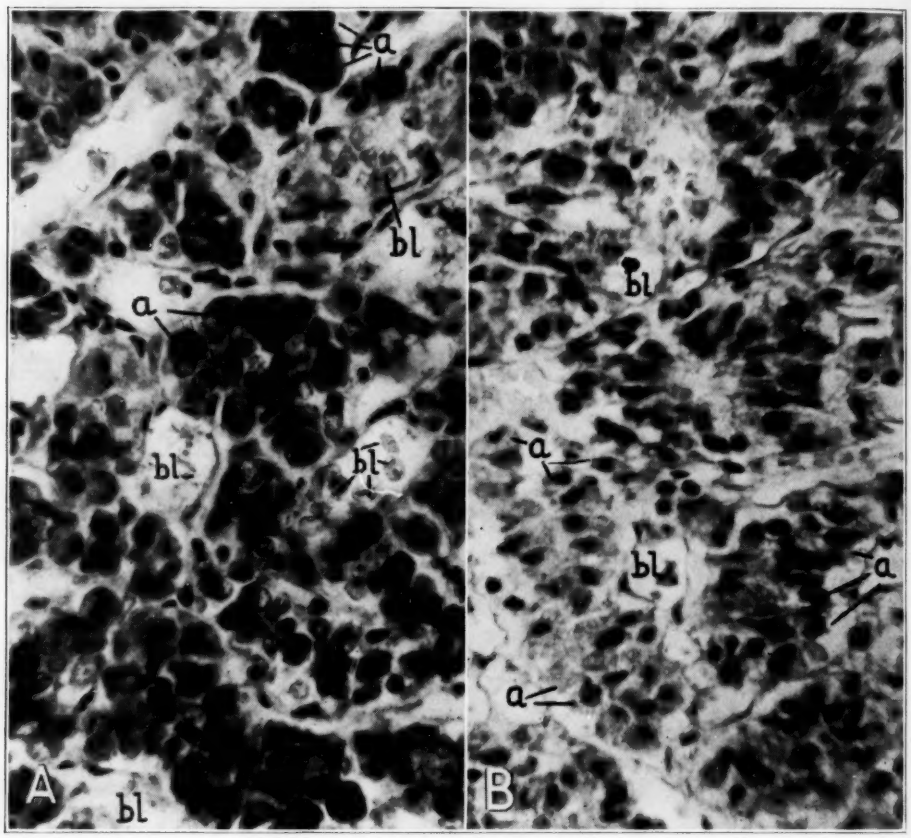

Fig. 3.—Cells of the anterior lobe in children with mongolism. Magnification, × 400.

A is taken from a 5 month old mongoloid boy (case 5), and *B*, from a 7 month old mongoloid girl (case 7). In both cases the anterior lobe was almost entirely composed of eosinophilic cells, with few chromophobic and no basophilic cells.

CASE 6.—*Six month old mongoloid girl.*

The anterior and posterior lobes were visible in horizontal sections. The two parts were separated by the cleft and were of nearly the same size. The posterior lobe was lined in the region of the cleft by a small layer of epithelial cells. The

cells were of primitive structure. They occurred among small connective tissue strips. There was little formation of glandular structure; no secretion could be recognized, and few connective tissue fibers were visible. The glia cells appeared scanty and underdeveloped.

The anterior lobe presented an amazing uniform picture: round cells, with dark blue chromatin, similar in type and equal in size. At many levels cells showed bright red protoplasm and were as small as those occurring in pregnancy. At other levels the chromophobic cells prevailed, but only small round nuclei were recognizable. Few chief cells of the large type were present. No basophilic cells were seen.

The blood spaces were enlarged and tightly packed with blood cells.

As a whole, the anterior lobe showed an increase of small eosinophilic cells and the presence of only one type of chromophobic cells: small round cells which are to be counted as immature acidophilic cells. There was complete lack of basophilic elements and of large chromophobic cells.

CASE 7.—*Seven month old mongoloid girl.*

The pituitary body weighed 0.101 Gm.; the frontal diameter was about 8 mm. The posterior lobe was very small. The anterior lobe consisted almost entirely of eosinophilic cells. These were small, but the red protoplasm was readily distinguishable. The nuclei were small and dark blue. In addition to these eosinophilic cells, piled in long lines along the blood spaces, a few chromophobic cells were visible. The nuclei were small and rich in chromatin. Basophilic cells and large chief cells were completely lacking (fig. 3 *B*).

CASE 8.—*Seven month old mongoloid boy.*

The pituitary body was very small and weighed only 0.065 Gm. The frontal diameter was 8 mm., and the sagittal diameter, 3 mm.

The gland was cut in serial sections from the ventral surface upward, so that about 600 sections on 100 slides could be studied. The gland was normally developed, especially the posterior lobe, which was not noteworthy. Its structure corresponded to that usually seen at this age. The pars tuberalis was developed. The anterior and the posterior lobe were separated by the cleft, which was still open.

The anterior lobe showed a rather uniform cellular composition. The acidophilic cells were developed and easily recognizable. Between them were large fields of cells which stained bluish violet with the Mallory stain. With this stain one had the impression that degenerated basophilic cells were present. However, with other stains, especially with alum hematoxylin and eosin, the presence of basophilic elements could not be proved, and all the cells, except the well developed eosinophilic cells, appeared as embryonic chief cells with small dark, blue nuclei embedded in a protoplasm which stained dark reddish blue.

CASE 9.—*Thirteen month old mongoloid boy.*

Sagittal sections showed a small posterior lobe lined by a few layers of epithelium in the region of the cleft, which was still open. There was little formation of tubular glands, with no signs of secretion. The anterior lobe was tightly packed with rather uniform cells, the round, equal-sized nuclei of which were densely piled and separated only by connective tissue and blood spaces, which appeared slightly enlarged. The eosinophilic cells were bright red, with nuclei containing bluish violet chromatin. Besides the eosinophils chromophobic elements belonging to the type of immature eosinophilic cells described in the other cases were visible. There were no basophilic or large chromophobic cells (fig. 2 *C*).

CASE 10.—*Eighteen month old mongoloid girl.*

Both lobes were present. They were so loosely connected that complete separation was easily made. The posterior lobe had a thin lining of epithelium and little formation of glandular structure. No colloid could be recognized. Development of fibers and glia seemed normal, and no abnormalities of this structure were observed.

The anterior lobe consisted of densely piled eosinophilic cells. The nuclei were round and rather large, much larger than those usually seen in eosinophilic cells. Around the nuclei the protoplasm stained bright red. These cells formed a dense conglomeration. In many fields only eosinophilic cells were visible. In other fields chromophobic cells were present among the eosinophils. The nuclei were similar to those of the eosinophilic cells, and only this chromophobic type was to be seen. No basophilic or large chromophobic cells were visible. Many free degenerated nuclei could be observed among the other cells. The whole gland consisted of eosinophilic cells and their immature forms.

CASE 11.—*Mongoloid girl aged 9 years and 8 months.*

The anterior and posterior lobes were well developed. The posterior lobe was separated from the anterior by the cleft, which was still completely open. There was much colloid in the cleft; it was brittle and formed many small crystals.

The structure of the posterior lobe did not reveal peculiarities. There were many glands, of the tubular-racemose type, filled with bright blue colloid. The epithelial wall was well preserved. The lymph channels showed a large amount of colloid, and even vessels near the posterior edge of the lobe carried colloid substances.

The anterior lobe was composed of the following types of cells: Both lateral fields were tightly piled with acidophilic cells, which were small but had brilliant red protoplasm. Among these acidophilic cells were some chromophobic cells, which were small and represented the immature acidophils. Few beta granules were present. They were bright blue and small.

The medial field of the lobe, between the sheets of connective tissue and near the anterior margin, was rather uniformly grayish blue. Study of the cells showed that they were chiefly arranged in tubules, which contained bright blue colloid. The cells were either chromophobic with a large amount of protoplasm, without granules, or smaller cells with cornflower-blue protoplasm. They lay in the connective tissue meshwork. Much colloid was to be seen within the spaces.

These cells belong histologically to the pars tuberalis, and I think it is safe to regard them as tuberal cells, although the place in which they were seen was not the usual location. It is beyond the limits of this paper to discuss this observation at length, but it may be mentioned that the same arrangement was noted in case 13. I am under the impression that this arrangement represents incomplete development of the pars tuberalis, which is derived from cell groups that are placed in the most anterior portion of the pars distalis. These cells usually embrace the stalk, but in some instances they keep their place around the anterior edge of the anterior lobe.

CASE 12.—*Ten year old mongoloid girl.*

The pituitary body was large and measured 11 by 10 by 4 mm. The weight was 1.1 Gm. After horizontal section of the gland it was obvious that the size and weight were due to a large colloid cyst, which filled the cleft and separated the lobes completely. The cyst was filled with brittle colloid, which splintered like glass when cut on the paraffin microtome. However, it was possible, with precaution, to secure a sufficient number of slides of the complete body for study.

The posterior lobe showed a small epithelial stratum, without many cells or formation of glands. The connective tissue fibers were coarse. Few glia cells were recognizable. A few larger channels, vertically arranged, and filled with blood, were visible. No absorption of colloid within the posterior lobe was recognizable. This may be of interest in regard to the large colloid cyst filling the cleft and to the fact that many small tubules of the anterior lobe showed bluish colloid similar to that which filled the cleft. One may suggest lack of absorption in the posterior lobe.

The anterior lobe was small. Its greatest sagittal diameter was 2 mm. The cells hung, cluster like, within the connective tissue meshwork. Most of them represented eosinophilic cells of a rather small type. The nuclei were dark blue and rich in chromatin. A small number of basophilic cells were recognizable. These cells were small and immature. The complete lack of chromophobic and mature basophilic elements was remarkable.

The pituitary body showed a large colloid cyst filling the cleft, with atrophy of the anterior lobe. The anterior lobe was composed mostly of eosinophilic cells, with some small basophils. No layers of reserve cells could be seen.

CASE 13.—*Twelve year old mongoloid girl.*

The pituitary body measured 11 by 10 by 4 mm. and weighed 0.3 Gm. The entire gland was cut horizontally in serial sections, from the stalk down. Anatomically, the whole pituitary body was interesting, for several reasons. In the upper part, where the anterior lobe was linked to the stalk, the anterior lobe was completely divided into two lateral lobes, while the medial part showed only connective tissue strands which kept the parts together. In the connective tissue meshwork of the trigonum Rogowitsch there were tubular elements, composed of small cells which stained blue or violet. These cells probably belonged to the pars tuberalis. The lateral lobes were surrounded with tuberal cells, which lined the entire margin, from the stalk to the anterior edge. At lower levels the trigonum Rogowitsch was better developed. The lateral lobes were tied together by connective tissue, which surrounded the whole lobe, and by a small layer of tuberal cells, which still embraced the lobe. They were recognizable even around the wall of the cyst, which lay between the lateral lobes of the pars distalis and was placed anterior to the trigonum Rogowitsch. Only caudad, near the end of the sacculus, was the anterior lobe complete. At this level it was separated from the posterior lobe by the cleft, which was still open. There was much colloid within the cleft.

The posterior lobe was worthy of consideration for two reasons: There were tubules of the tubular-racemose type; near the center of the lobe a large amount of colloid was visible, which is unusual so near the center. There were also tubular formations rather deep within the lobe. Colloid was seen even in the vessels around the posterior lobe.

The anterior lobe, at the caudal end of the sacculus, showed many eosinophils scattered over the whole horizontal section. They stained bright red, were rather small and had a small nucleus. These cells were scattered over a field which appeared to be grayish blue. Analysis of this field of "reserve cells" showed many cells the protoplasm and chromatin of which stained blue. The nuclei were small and did not differ in size from those of eosinophils. Some of these cells may have been small basophilic cells.

At a higher level the composition of the anterior lobe differed from that near the caudal end. At higher levels the acidophilic cells formed gross fields in both lateral sections. In these fields only a few immature basophils were recogniz-

able. The middle field of the pars distalis was formed by a coarse network of connective tissue. Within the holes of this network groups of small cells were visible. They must be considered as tuberal cells.

It is noteworthy that the sacculus of the anterior lobe abounded in colloid. All spaces were tightly packed with a bright blue homogeneous mass, which appeared to be similar to the colloid in the cleft.

CASE 14.—*Thirty year old mongoloid man.*

The pituitary body was round, measured 10 by 10 mm. and weighed 0.9 Gm. Horizontal sections of the body showed well developed anterior and posterior lobes. The posterior lobe was rich in connective tissue; the vessels were marked and rather congested. The glial meshwork did not show peculiarities. Near the caudal end tubules, walled with high epithelium, contained an indistinct secretion described by some authors as mucin. Besides these glands, a few acini were visible walled with flat epithelium and tightly packed with colloid. No colloid was seen in the cleft. Noteworthy is the fact that the posterior lobe contained some eosinophilic cells. No basophilic cells were present.

The caudal section of the anterior lobe was entirely filled with eosinophils. They were small, with small nuclei and bright red protoplasm. They were either arranged in dense piles or lined up, along the strands of connective tissue, and the formation was somewhat similar to the picture described as eosinophilic "adenoma." There were no other eosinophilic types and no basophils, and only few immature chromophobic cells could be recognized (fig. 2*D*).

At higher levels the picture differed a little from the preceding description. There was overdevelopment of connective tissue strands radiating through the anterior lobe. The cellular composition was simple; both lateral areas were almost completely composed of small eosinophilic cells. They were densely piled or lined up, and the picture was the same as that near the caudal end of the lobe. In the middle field there were some immature cells in the meshwork of connective tissue. They were small and of indefinite reaction. There was no invasion of basophils into the eosinophilic areas at each side.

The anterior lobe showed an increase in eosinophilic cells, with complete lack of chromophobic and basophilic cells. There was invasion of eosinophilic cells into the posterior lobe.

SUMMARY OF OBSERVATIONS

To facilitate understanding of the observations previously given in detail, I present in table 1 a survey of the 14 cases. The table reveals that case 3 differed from the others. Sections of the pituitary in this case were received with only the remark: "Mongoloid girl, 2 months old." I did not study the history before microscopic examination, in order to avoid prejudice. Not before repeated comparisons were made of material in this case with that in the other cases was it decided that this case must have been clinically different. Study of the history revealed that the diagnosis, that of mongolism, was a guess, expressed at the beginning of clinical observation, and that it had already been abandoned by clinicians and the pathologist at autopsy.

The child was born prematurely and died at the age of 2 months. The weight at birth was 3 pounds and 9 ounces (2,523 Gm.). The length of the body at

autopsy was 43 cm. The head was reported to be large, but, unfortunately, exact measurements were not available. On further inquiry, my assumption that this child was not a mongoloid was verified.

I included the case to demonstrate that, in my opinion, the pathologic changes of the pituitary body in mongolism are so definite that a normal picture at autopsy would cast doubt on the diagnosis of mongolism.

Cases 2 and 4 are somewhat different from those which will be discussed later. In both cases the pituitary was composed almost entirely of embryonic chief cells. They showed small nuclei, rich in

TABLE 1.—*Summary of Data in 14 Cases of Mongolism*

Case	Age	Sex	Size of Pituitary, Mm.	Weight of Pituitary, Gm.	Acidophils	Basophils	Embryonic Chief Cells	Large Chromophobic Cells	Arrangement of Cells
1	2 days	F	5 (front diameter)	.....	++	Few, immature	+++	Few	Glandular
2	6 wk.	F	.....	.....	—	Few, amphoterous	+++	—	Piled densely; columnar
3	2 mo.	F	.....	.....	Normal	Normal	—	Normal	Normal
4	3 mo.	M	.....	.....	—	Few, amphoterous	+++	—	Piled densely; irregular
5	5 mo.	M	6×5	0.085	Large, +++	—	+	—	Tubular
6	6 mo.	F	.....	.....	+++	—	+++	—	Irregular
7	7 mo.	F	8 (front diameter)	0.101	+++	—	+	—	Tubular; adenomatous
8	7 mo.	M	8×3	0.065	++	Few, amphoterous	+++	—	Irregular
9	13 mo.	M	.....	.....	++	—	+++	—	Irregular
10	18 mo.	F	7 (front diameter)	.....	++	—	+++	—	Irregular
11	9 yr., 8 mo.	F	11×9×6	0.3	+++	Immature, +	+	+	Irregular
12	10 yr.	F	11×10×4	1.1	+++	Few, immature	—	Few	Clustered
13	12 yr.	F	14×10	0.3	+++	Few, immature	+++	—	Adenomatous
14	30 yr.	M	10×10	0.9	+++	—	++	—	Adenomatous

chromatin, and therefore stained deep blue. There was little protoplasm about the nuclei. This protoplasm stained violet blue with the Mallory stain. In contrast to observations in the following cases, there were cells in these cases with blue protoplasm of a definite nature. These cells seem to be true basophils. However, it was not possible to prove this impression by using different methods. Hematoxylin or the Dominici method stained these cells like embryonic chief cells. Unfortunately, it was not possible to try the Masson-Severinghaus method. As a whole, the pituitary in these cases showed retarded development and general degeneration. Such an observation is not contradictory to the picture in the next group, but is not typical of mongolism.

I shall now summarize the group of cases 1, 5, 6, 7, 8, 9 and 10. These were cases of children between 2 days and 18 months of age. In previous papers repeated emphasis was placed on the time factor. According to the assumption that mongolism occurs during fetal life and is already present at birth, observations in cases of very young children are of most interest.

In this group of cases the changes were amazingly uniform. In all the pituitary gland was rich in eosinophilic cells, and lacked completely basophilic and large chief cells. If chromophobic cells were present, only the small type of immature embryonic cells was to be seen. The pituitary in these cases revealed a definite lack of the basophilic system. Eosinophils abounded, but no signs of hyperactivity could be recognized. The abundance of eosinophils seemed to be due to a lack of basophils rather than to an overgrowth of the eosinophilic cells. There were no definite signs of adenomatous growth, and the small size of the pituitary, as a whole, seemed to rule out such pathologic activity. On the other hand, the lack of basophilic and chief cells was striking. Normally, though less numerous than eosinophils, they are expected to be present after birth. They form an important element in the composition of the anterior lobe, and lack of these cells reveals definite failure in development.

The next group of cases includes those of 3 girls aged 9, 10 and 12 years, respectively; the 3 patients were similar in appearance—stout, fat and pronouncedly mongoloid. It is interesting to see what happens when the mongoloid child survives the first two critical years of life. In these cases the pituitary showed abundance of eosinophils; their number seemed definitely increased. The glands were abnormally rich in colloid. In case 12 there was a large colloid cyst, with atrophy of the anterior lobe. In cases 11 and 13 a large amount of brittle colloid was present in the cleft and in the posterior and the anterior lobe, in which the colloid filled all spaces between the glandules. I do not know whether abundance of colloid has any significance, but it may be worth keeping in mind.

In these cases there were few basophils and chief cells, but their type was less developed than in the normal gland. There was little mingling of basophils in the areas occupied by eosinophils.

The last case is that of a man aged 30. He was poorly developed and underweight. The length of the body was 142 cm.; the weight was 79 pounds (35.8 Kg.). The skull was 50.2 cm. in circumference; its length, 17 cm., and its width, 14.8 cm. There was no axillary hair; long silky pubic hairs were present. The testes were descended; the penis was small and infantile. Of the observations at autopsy, it may be mentioned that the thyroid weighed only 7.6 Gm. (expected weight,

about 30 Gm.). Both thyroid lobes showed enlargement of the vesicles and desquamation. The changes were recorded as "involutional." Some thymus tissue was still recognizable—the gland weighed 4 Gm. The testes weighed 3.7 and 2.3 Gm., respectively; they were definitely atrophic. Microscopically, they showed edema and increase of intertubular tissue. The tubules were atrophic, and no spermatogenesis was present.

The histologic appearance of the pituitary body was remarkable. There was a definite increase in eosinophilic cells, with complete lack of basophilic and chromophobic elements. The cells showed an adenomatous arrangement.

Comment.—From a survey of the observations on persons with mongolism it is obvious that a special type of alteration in the pituitary body corresponds to the clinical picture of this condition. In all cases in which the diagnosis is true mongolism there is definite deficiency of the basophilic system. It is remarkable that the eosinophilic system is not affected in the same way, and I wish to emphasize that the specificity of the pathologic condition seems to lie in that fact. General degeneration of the pituitary body, with equal degeneration of all types of cells, may be produced by many diseases, but a specific deficiency of the basophilic system is not yet recognized. I observed this lack of basophils and large chief cells without exception. In adults with mongolism a slight development of basophils may occur, but they differ from the normal. They never reach maturity, such as was seen in the controls, even in the first years of life. Therefore, the conclusion seems to be justified that mongolism is associated with a deficiency in the basophilic system of the anterior lobe.

GENERAL COMMENT

Two main problems will be discussed: the relation of the pituitary to other endocrine glands, and the general significance of the basophilic deficiency in mongoloid persons.

With regard to the first point, it is known that the structure of the anterior lobe is extremely sensitive to changes in the endocrine equilibrium of the organism. Changes in other glands may produce alterations in the anterior lobe. Especially interesting is the dependence of the anterior lobe on the gonads and the thyroid. I have spent much time on a study of the gonads in mongoloid patients and shall publish the observations at a later date. For the moment, it may be sufficient to state that at the time when alterations in the pituitary are already recognizable the development of the gonads is still progressing. This makes me think that changes in the gonads, if observed, are not the

cause of pathologic changes in the anterior lobe. This allusion may be sufficient for the present.

More difficult is the question of the relation between the thyroid and the pituitary. I have already reported [1] on the alteration in the thyroid; it is worthy of consideration whether these changes may explain the pathologic picture in the pituitary. Many experimental studies have been reported in the literature regarding the interrelationship of the two glands. Trautmann [2] first reported the results of a study of the pituitary body after thyroidectomy in goats. He recorded increase in connective tissue of the pars nervosa, increase in pigment and striking alteration of the chief cells in the pars anterior. The chief cells were principally affected, and few were to be seen a few weeks after thyroidectomy. The basophils were not altered, and he reported that these cells are the most resistant elements in the pituitary body. The eosinophilic cells seemed to be increased in number. These changes were recognizable after total thyroidectomy. If residual or accessory thyroid glands were present, the changes were not observed or were less marked. These experiments of Trautmann have been repeated by many authors and generally confirmed. Some authors observed enlargement of the pituitary in conditions of dysfunction of the thyroid. This statement is not generally accepted, but it seems certain that enlargement rather than decrease in size can be more commonly observed after thyroidectomy.

I believe that the histologic changes in mongolism differ from the alterations seen after complete thyroidectomy and that the pathologic changes in mongolism do not depend on lack of thyroid.

General experience with alterations of the hypophysis in conditions of hyperthyroidism is not as well established. Some authors have reported changes, but their results have not been generally accepted. Such recorded alterations were increase in number of eosinophils and increase in size of the whole gland. In animals, Romeis [3] observed after stimulation of the thyroid the appearance of a special type of cell in the pituitary, the so-called struma cell. This cell was also seen by MacCallum and Schilder.

Extensive clinical experience is also against the idea that hyperthyroidism or hypothyroidism during pregnancy is sufficient in itself to cause mongolism.

For the dependence of changes in the thyroid on alterations in the pituitary more clinical evidence exists. In 1902, Carl Benda, in his

1. Benda, C. E.: Studies in Mongolism: II. The Thyroid Gland, Arch. Neurol. & Psychiat. **41**:243 (Feb.) 1939.

2. Trautmann, A.: Hypophyse und Thyroidectomie, Frankfurt. Ztschr. f. Path. **18**:173, 1916.

3. Romeis, B.: Ueber die Veränderungen der Hypophysis bei Erkrankungen der Schilddrüse, Virchows Arch. f. path. Anat. **251**:235, 1924.

paper on acromegaly,[4] emphasized that struma and myxedematous degeneration of the thyroid are to be observed with equal frequency in cases of acromegaly. Cushing [5] called particular attention to alterations of the thyroid in relation to diseases of the pituitary. He produced experimentally both cellular desquamation and hyperplasia in the thyroid of the dog after total extirpation of the hypophysis. He noted increased proliferation of thyroid epithelium with dissolution of colloid and other signs of acute hyperplasia. Chromophobic elements, colloid cysts and increase of connective tissue were common. Cushing stressed repeatedly the bizarre types of nuclei often seen in rapidly progressing hyperplasia and mentioned many instances of chromophobic struma in his cases of acromegaly.

In a recent publication on experimental pituitarectomy, Putnam, Benedict and Teel [6] demonstrated the same type of alteration of the thyroid.

In 1927 Cushing, in collaboration with Davidoff,[7] again dealt with the pathologic changes in acromegaly. In this masterly paper the endocrine pathology finds special reference. It is amazing how deeply the whole endocrine system is involved in acromegaly, as Cushing emphasized in the report of his first case:

> A persistent thymus, a large colloid goitre, enlarged parathyroids, hypertrophy of the pancreas and greatly hypertrophied adrenals due to an adenomatosis of the cortical substance. To any one of these markedly changed glands, an observer might in the 1880's have ascribed the malady with greater seeming probability than to the normal-sized hypophysis.

Indeed, in all cases of pituitary disease, especially acromegaly, the alterations are not restricted to the pituitary body. I may again cite Cushing's introduction.

> However, hyperpituitarism is not so simple a matter as is hyperthyroidism in which the essential lesion is restricted to the thyroid and the secondary pathological alterations of other organs are of minor consequence. In acromegaly, on the contrary, the gross secondary changes in other organs are manifold and constitute one of the amazing features of this kaleidoscopic disorder.

Regardless of the striking endocrine disorder in acromegaly, most observers agree that acromegaly is due to an eosinophilic adenoma of the pituitary body.

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4. Benda, C.: Akromegalie, Deutsche Klin. **3**:261, 1902.

5. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

6. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly: VIII. Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Pituitary, Arch. Surg. **18**:1708 (April) 1929.

7. Cushing, H., and Davidoff, L. M.: Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, 1927.

It is attractive to compare two such different conditions as acromegaly and mongolism. In both the general endocrine disorder is amazing. The thyroid shows histologically the picture of colloid or parenchymatous goiter, but in mongolism there is no increase in size of the gland. Moreover, decrease may be noted. The testes show the atrophy typical of many diseases of the pituitary. With regard to the ovaries: Cushing observed four large, fully developed graafian follicles in the ovary of an acromegalic woman aged 26, who had amenorrhea. I examined the ovary of a 12 year old mongoloid girl that showed five cystic follicles, without ova (fig. 4). The membrana granulosa was lifted from the theca interna, but neither the granulosa nor the theca was degenerated, nor were the follicles collapsed. Menstruation had not

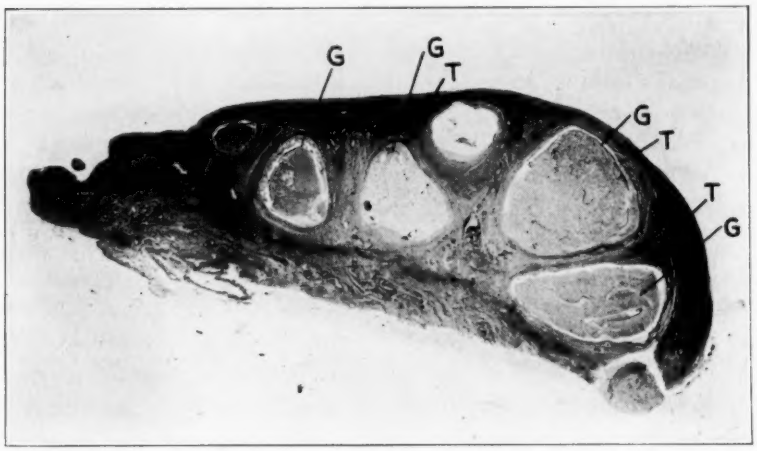

Fig. 4.—Ovary of a 12 year old mongoloid girl. Magnification, × 3.3. *G* indicates the membrana granulosa, and *T*, the theca. The picture shows five enlarged follicles. They are lined by the theca interna and a perfectly preserved membrana granulosa. The latter is lifted from the theca at some points and is floating, but not degenerated. No eggs were seen in the follicles. Normally, the membrana granulosa degenerates after ripening of the egg, and the follicle becomes atretic. In this case normal involution failed, and the follicles became "true cysts." Clinically, there was no menstruation.

been observed. It may be well to keep in mind that the clinical picture of pituitary diseases is not due merely to the pathologic condition of the pituitary. It seems more reasonable to assume that the disturbance of the endocrine balance, with uncontrolled stimulation or retardation, may produce the striking disorders which are observed in acromegaly or mongolism.

With regard to the latter, I have already emphasized [1] that the alterations of the thyroid may play an important role in the mechanism of mongolism. I wish to add that a primary disorder of the pituitary body

appears to be the cause of the general endocrine disorder. The essential alteration that is associated with mongolism, it seems to me, is the deficiency of the basophilic system of the anterior lobe. Although I observed increase of eosinophilic cells and called attention to the fact that in case 14 the picture could easily be mistaken for an eosinophilic adenoma of the pituitary body, I do not believe that hyperpituitarism plays a role in this condition.

In table 2 is a brief survey of the various diseases which are related to changes in the anterior lobe of the hypophysis. It is presented merely as a working program.

Although some relation between the growth hormone and eosinophils and the "sex hormone" and basophils, respectively, seems to be accepted,

TABLE 2.—*Relation of Various Diseases to Changes in Anterior Lobe of the Pituitary*

Pathologic Picture	Symptom	Disease
Overgrowth of eosinophils	Pathologic growth of the body	Acromegaly
Overgrowth of basophils	(1) Hypertension; partial fat dystrophy	Cushing's disease
	(2) Hyperplasia endometrii pituitaria	Hofbauer's disease
Overgrowth of chief cells (?)	Adiposity; genital dystrophy	Dystrophia adiposogenitalis of Fröhlich
Congenital dysfunction of anterior lobe	Growth disturbance; genital dystrophy; mental deficiency	Mongolism
Temporary dysfunction of anterior lobe in infancy	Retardation of growth	Infantilism
Destruction of anterior lobe in later life	Cachexia	Simmonds' disease
Deficiency of eosinophils in infancy	Dwarfism	Nanosomia pituitaria
Deficiency of basophils	Sexual infantilism	Eunuchoidism; adiposity

it is still unknown which cells produce the many hormones which physiology now relates to the pituitary body. The tuberal system, which seems to be of importance from an anatomic point of view, has not been mentioned at all in table 2.

With regard to the problem of mongolism, I expect that this deficiency may find its place among the pituitary disorders. Deficiency of the basophilic system, increase in eosinophils, lack of reserve cells as a whole and disturbance of the composition of the anterior lobe characterize this type of mental deficiency, which plays the greatest role among the various types of growth disorders.

CONCLUSIONS

It has long been thought that in mongolism pituitary disorder plays an important part. Timme [8] expressed this belief and based his therapy

8. Timme, W.: Mongolism and Its Treatment, Bull. Massachusetts Dept. Ment. Dis. **14**:229, 1930.

on the assumption. He asserted that roentgen examination of mongoloid persons shows enlargement of the anterior part of the sella turcica, occasionally with pressure on the optic nerves. Although this change is not thought to be typical of mongolism, it indicates that enlargement of the sella is produced by an increase in the pituitary body. My pathologic studies do not corroborate such an interpretation. With 1 exception, I found a small pituitary body in persons with mongolism. The abnormality of the skull base, which was recorded in my first paper,[9] seems to me to be produced by a general disturbance of growth rather than to be the direct effect of pressure from an enlarged pituitary body.

The only histologic study of the pituitary in cases of mongolism was recorded by Gordon,[10] who studied 2 cases of the disease. The first was that of a girl aged 14 months. The pituitary body was "very rich in eosinophile cells and seem[ed] well vascularized." The second case was that of a girl aged 6 weeks.

> The gland cells of the anterior lobe are rather small, particularly in the periphery. The capillaries between the gland cells are rather wide, sinus-like and lined by conspicuous reticulum fibrils and cells. Occasionally there is a homogeneous faintly staining substance around the capillary separating the latter from gland cells. The gland cells are better maintained in the center of the organ; there the eosinophiles are conspicuous while the basophiles are absent. A small cyst filled with colloid separates the anterior from the posterior lobe. The latter consists of dense nervous tissue with few nuclei.

Gordon did not discuss the significance of his observations, but they correspond to my own.

Sometimes, in the literature the presence of a "normal pituitary" is mentioned without evidence that adequate methods were used. Such reports must be disregarded.

The 13 cases of mongolism which I have reported seem to me to be sufficient evidence from which to conclude that mongolism is associated with a pituitary disorder, particularly an insufficiency of the basophilic and chief cell system. I believe that the alterations of other endocrine glands observed in mongolism depend on the deficiency of the pituitary body.

I do not wish to close the discussion without calling attention to a problem which may be considered an objection to the significance of the observations presented. Embryology teaches that one must distinguish between morphogenesis and morphokinesis. Morphogenesis is the evolution and development of form; morphokinesis is the stimulation of such development. Morphokinetic factors influence the time at which devel-

9. Benda, C. E.: Studies in Mongolism: I. Growth and Physical Development, Arch. Neurol. & Psychiat. **41**:83 (Jan.) 1939.

10. Gordon, M. B.: Morphological Changes in the Endocrine Glands in Mongolian Idiocy with Report of Two Cases, Endocrinology **14**:1, 1930.

opment is carried on and produce the right rhythm. Morphogenesis is due to endogenous factors. The endocrine glands are a late ontogenetic acquisition regulating morphokinesis. This distinction between morphokinetic and morphogenetic factors, which may seem of only theoretic interest, is important in the determination of developmental disorders. The question arises: Is mongolism a morphogenetic monstrosity or a morphokinetic disturbance? If the former is true, and the presence of idiocy, epicanthal fold, slanting eyes and deformity of the skull is an accidental combination of various malformations, then mongolism is a monstrosity due to germinal deterioration and not to endocrine factors. Mongolism, as a monstrosity, would be completed before endocrine functions begin their influence.

On the other hand, if mongolism is a morphokinetic disorder, endocrine factors are of decisive influence. It is beyond the limits of this discussion to enter again into details. It may be kept in mind that in mongolism developmental deformities which point to the first months of fetal life are extremely rare. It is of importance to recognize that the earliest stages of development seem to pass without failure ("teratogenetic determination," Schwalbe).

In summarizing the discussion, it may be emphasized that there is much evidence to indicate that in mongolism one deals with a morphokinetic abnormality due to an endocrine imbalance, and not with a morphogenetic monstrosity.

Another question is: Can the pituitary of the embryo be responsible for the failure of development in mongolism? Endocrine functions start rather late in fetal development. There is much discussion as to how powerful such an influence is.[11] The pituitary body of the embryo is thought to begin secretion in the sixth month of fetal life (Schlimpert). The first appearance of eosinophilic cells has been mentioned as occurring in the fourth month of fetal development (Berblinger, Pietsch). On the other hand, it is known that the maternal pituitary is enlarged during pregnancy. The tax on the maternal gland during pregnancy is great. Bruehl and Philipp[12] have demonstrated that pituitary secretions of the mother pass the placenta into the embryo. The amount of this supply is so remarkable that three days after birth it is still demonstrable in the urine of the child. There is some suggestion that insufficiency of the maternal pituitary may play a role. Deficiency of the pituitary in mongolism may be due to failure of maternal supply. In order to decide this question, new investigations are needed. Only a study of miscarriages

11. Thomas, E.: Innersekretorische Drüsen bei Feten und Kindern, in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1933, vol. 2, p. 1291.

12. Thomas,[11] p. 1294.

and stillbirths can bring about a solution, and it would be of great help if obstetricians and pathologists would take an active interest in these problems.

SUMMARY

1. The present study deals with the microscopic examination of the pituitary bodies of 14 supposedly mongoloid patients.

2. The histologic pictures in 13 cases of mongolism and in 1 case of premature birth are presented. In the 13 cases of mongolism definite alterations peculiar to this condition were invariably observed.

3. The alterations consist in an increase of eosinophilic cells and a deficiency of basophilic and chief cells. In analyzing these alterations, the question is discussed whether the increase of eosinophilic cells or the absence of basophilic cells has the greater pathologic significance. Because the size of the pituitary is not increased and no signs of eosinophilic hyperactivity are found, the absence or deficiency of basophilic cells appears to be the most important observation. This deficiency seems to be characteristic of and definitely associated with the clinical picture known as "mongoloid deficiency."

4. In discussing the significance of the observations, the difference between morphogenetic and morphokinetic factors is emphasized. There are many indications that mongolism is the result of a morphokinetic failure and is due to an endocrine disturbance. The key to the general disorder seems to be a particular pituitary deficiency, which may be due to a pituitary deficiency of the mother during pregnancy. The advanced maternal age, frequently observed in cases of mongolism, and other factors indicate that the maternal organism is not apt to adjust itself to a new pregnancy. Further studies in this direction are under way.

VISUAL DISTURBANCES ASSOCIATED WITH TUMORS OF THE TEMPORAL LOBE

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There were 292 cases in which a diagnosis of tumor of the temporal lobe was made at the Mayo Clinic prior to 1937. In 211 of these the diagnosis was verified by biopsy of the tumor, by necropsy or by removal of typical gliomatous cystic fluid. These 211 cases are the basis of the present study, which is concerned only with the visual disturbances in such cases. Studies of other aspects of the symptomatology and diagnosis, based on the same series of cases, will be presented in later publications. A statistical analysis has been made of all the signs and symptoms which the patients displayed. The microscopic slides of the specimens obtained at biopsy have been reexamined. Necropsy specimens of the brains of 52 of the patients were obtained and examined in an attempt to correlate the associated signs and symptoms with the situation, size and type of each tumor.

Several series of such cases have been reported in the literature, but there remain debatable points about the symptomatology of this group of tumors and the anatomic relations of the region in which they occur. The disturbances pertaining to vision are of special interest because of the many differences of opinion regarding their interpretation and diagnostic value. Certain kinds of hallucinations, certain types of visual field defects, inequality of the pupils, ptosis, differences in the degree of choked disk in the two eyes and other disturbances of the visual apparatus have been assigned varying degrees of importance by different clinicians. A few are still skeptical of the diagnostic value even of visual field defects.

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* Fellow in Neurology and Psychiatry at the Mayo Foundation at the time this work was done.

A portion of the material in this paper was used by Dr. Sanford in preparation of a thesis submitted to the Faculty of Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in neurology and psychiatry.

With regard to the anatomic relations of the visual pathways, there is disagreement over certain details, knowledge of which is of diagnostic importance in the interpretation of defects of the visual field. Two anatomic questions of particular interest are: 1. Do the visual neurons, after leaving the external geniculate body, detour anteriorly about the inferior horn of the lateral ventricle in the manner described by Meyer?[1] 2. Is each half of each retinal macula represented bilaterally in the cortex of the occipital lobe? Part of the object of this study was to obtain evidence on which to base answers to these questions and to evaluate such answers with regard to their importance in differential diagnosis and in exact localization of tumors of the temporal and occipital lobes.

Enough sound evidence has been accumulated in the past to justify the belief that the various groups of neurons which conduct impulses from well defined regions of the retinas follow a systematic change in their anatomic relations from their beginnings in the retinas to their endings in the occipital lobes. This arrangement gives a systematic representation of these retinal regions, namely, the maculas, the various retinal quadrants and the unpaired, peripheral nasal retinal crescents, at successive levels in the visual pathways, back to and including the striated areas. It also suggests a similar representation of the finer retinal details, but the evidence for this is inconclusive. Exact knowledge of the different anatomic relations of the aforementioned groups of neurons at various levels in the visual pathways is of clinical importance, because with it definite defects in the visual fields can be correlated with lesions at definite levels. Much of this knowledge is well established and part of it will be reviewed here in order to insure better understanding of the present problem.

In each optic nerve, immediately behind the eyeball, the group of fibers from the macula lies as a wedge on the lateral aspect. The groups representing the various retinal quadrants are arranged in a manner roughly corresponding to their retinal origins, while the fibers from the unpaired nasal periphery lie along the medial aspect. On approaching the optic chiasm, the macular group lies more centrally. After the decussation of the nasal fibers in the chiasm, the crossed fibers at first lie ventrally, and the uncrossed fibers dorsolaterally, in the optic tracts. Just in front of the external geniculate body, the crossed and the uncrossed fiber groups become arranged in alternate layers. Here the groups representing the various retinal regions make a rotational change in their positions of approximately 90 degrees about the axis of the optic tract, so that the fibers from the homonymous upper retinal

1. Meyer, A.: The Connections of the Occipital Lobe and the Present Status of the Cerebral Visual Affections, Tr. A. Am. Physicians **22**:7-16, 1907.

quadrants lie medially and those from the lower quadrants laterally. The wedge of homonymous macular fibers then occupies the upper pole of the tract and the group of unpaired fibers the lower pole.

This arrangement of the various groups of fibers just before they enter the external geniculate body apparently determines grossly the arrangement of their respective synapses in this ganglion. The lateral geniculate bodies are composed of alternating light and dark bands, and in these the synapses of the crossed and uncrossed fibers alternate. There are more synapses for the crossed fibers anteriorly and for the uncrossed fibers posteriorly. The synapses for the macular fibers are more numerous posteriorly. From the lateral geniculate bodies, the final neurons in the visual pathways continue posteriorly as the geniculocalcarine fasciculus, to terminate in the calcarine cortex of the occipital lobe.

It is the course of the final neurons of the visual pathway that interests us primarily, for it is mainly this part of the pathway which is associated with the temporal lobe. For many years it was thought that these neurons, as originally described by Gratiolet, left the lateral geniculate body and proceeded backward in a more or less straight line to their terminations in the occipital cortex. In 1907, Meyer [1] reported 2 cases of mental disturbance associated with organic disease of the brain in which the parietal, temporal and occipital lobes on one side had been destroyed, leaving the optic radiations in "pure culture." After studying these brains he was convinced that part of the optic radiation, after leaving the lateral geniculate body, reverses its course and, instead of running backward toward its destination in the occipital lobe, turns forward, passing anteriorly for a short distance in the temporal lobe to arch around the inferior horn of the lateral ventricle and then turn backward. The ventral fibers pass farthest forward before they turn back, while some of the most dorsal fibers do not take the forward turn at all but start directly back toward the visual cortex (fig. 1).

Although this loop forward in the visual pathways is now commonly referred to as Meyer's loop, Meyer disclaimed credit for it, saying that it was originally described by Flechsig. About the time of Meyer's report, Archambault [2] showed that these terminal neurons occupied not the internal sagittal lamina, as was generally accepted, but the external sagittal lamina. This agreed with a suspicion previously expressed by

2. Archambault, L.: The Inferior Longitudinal Bundle and the Geniculo-Calcarine Fasciculus: A Contribution to the Anatomy of the Tract-Systems of the Cerebral Hemisphere, Albany M. Ann. **30**:118-143 (Jan.) 1909.

Sachs.[3] It also has been confirmed more recently by Putnam [4] in a careful pathologic study. Archambault also said that for this part of the visual system the term "optic radiation" was unsatisfactory and proposed the use of the term "geniculocalcarine fasciculus." Of the various names applied to this unit of the pathways, this is considered the most appropriate.

Cushing and Heuer,[5] in 1911, reported the case of a patient with a gunshot wound in the temporal lobe. Perimetric examination disclosed a small homonymous upper quadrantic defect in both fields of vision. This suggested to Cushing that there undoubtedly had been overlooked in the past an important sign in the diagnosis of tumors of the temporal lobe. From then until 1933, he saw 59 cases in which such a diagnosis

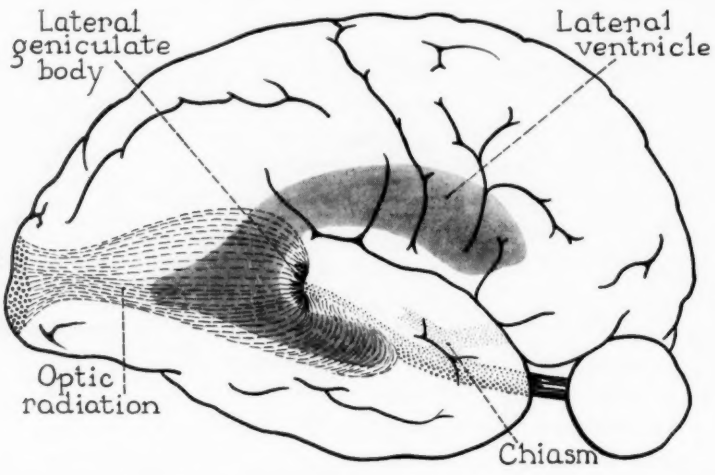

Fig. 1.—The temporal lobe detour, the so-called Meyer's loop in the geniculocalcarine fasciculus (adapted from Cushing [6]).

was made.[6] In 39 cases of this group a careful perimetric field examination was possible. Of these, results of the examination were normal in 6 cases; homonymous hemianopia was present in 8, and a homonymous

3. Sachs, H.: Das Gehirn des Förster'schen Rindenblinden, Arb. a. d. psychiat. Klin. in Breslau, 1895, no. 2, pp. 53-104.

4. Putnam, T. J.: Studies on the Central Visual System: II. A Comparative Study of the Form of the Geniculostriate Visual System of Mammals, Arch. Neurol. & Psychiat. **16**:285-300 (Sept.) 1926.

5. Cushing, H., and Heuer, G. J.: Distortions of the Visual Fields in Cases of Brain Tumor: Statistical Studies, Bull. Johns Hopkins Hosp. **22**:190-195 (June) 1911.

6. Cushing, H.: Distortions of the Visual Fields in Cases of Brain Tumor: The Field Defects Produced by Temporal Lobe Lesions, Tr. Am. Neurol. A., 1921. pp. 374-420.

quadrantic defect was present in 25. These observations suggested that when homonymous quadrantic anopia is found a tumor of the temporal lobe should be suspected.

It was not long before this work of Cushing's was opposed. Traquair,[7] and later McConnell,[8] stated that in their opinion there was no forward detour in the fibers as had been described by Meyer. They further expressed the belief that tumors in the temporal lobe, anterior to the level of the lateral geniculate body, cause field defects not by interference with the geniculocalcarine fasciculus but by pressure downward on the optic tract. The chief reason for this belief was that field defects caused by tumors of the temporal lobe are often incongruous; that is, although homonymous, the defect in the field of one eye is larger than, or does not match, that in the field of the other eye. Traquair insisted that such defects must be the result of interference in the optic tract, not in the radiation, for after the lateral geniculate body is reached the fibers from corresponding retinal points are thought to be side by side and a lesion interfering with one must also affect the other. Thus, the visual field defects produced must be congruous. Kravitz[9] stated that he subscribed to this belief, but his reasoning is difficult to follow. It was stated further by Traquair that the forward looping described by Meyer could not be demonstrated anatomically. It is true that it cannot be seen in the dissection of a normal brain but appears only in such fortunate circumstances as those which prompted Meyer to announce its presence. Pfeifer[10] satisfied himself that it is an anatomic entity.

Furthermore, from more advanced knowledge of the minute anatomic structure of the lateral geniculate bodies, it is now known that it is not safe to assume that incongruous field defects must always be caused by a lesion in the system anterior to the geniculate bodies. As has been stated previously, the crossed fibers have their synapses anteriorly in each lateral geniculate body and the uncrossed fibers posteriorly. As the neurons of the geniculocalcarine fasciculus leave the geniculate bodies, they spread out fanlike in a general lateral direction, forming what is referred to as the "optic peduncle." For a short distance in

7. Traquair, H. M.: The Course of the Geniculo-Calcarine Visual Path in Relation to the Temporal Lobe, Brit. J. Ophth. **6**:251-259 (June) 1922.

8. McConnell, A. A.: Fields of Vision in Connexion with Intracranial Lesions, Brit. M. J. **2**:226-228 (Aug. 5) 1933.

9. Kravitz, D.: Value of Quadrant Field Defects in Localization of Temporal Lobe Tumors, Am. J. Ophth. **14**:781-785 (Aug.) 1931.

10. Pfeifer, R. A.: Myelogenetisch-anatomische Untersuchungen über den zentralen Abschnitt der Sehleitung, in Foerster, O., and Wilmanns, K.: Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie, Berlin, Julius Springer, 1925, no. 43.

this peduncle the crossed fibers are anterior and lateral and the uncrossed fibers posterior and medial. An interruption in this area would cause an incongruous defect, and, as reasoned by one of us (H. L. B.),[11] if the pressure is from the lateral aspect the larger defect should be expected in the field of the contralateral eye.

It is known that in visual fields having homonymous hemianopia associated with tumors of the occipital lobe there are often areas of varying size around the fixation point in which there is retention of vision in the otherwise blind halves of the fields, the so-called sparing of the macula. The reasons offered to explain this phenomenon are numerous, the one causing the most controversy being that each half of each macula is represented in both occipital lobes. Sparing of the macula does not occur as frequently in cases of tumor of the temporal lobe as in those of tumor of the occipital lobe. It was supposed, therefore, that in one temporal lobe all the macular fibers from homonymous halves of the fields could be interrupted by a single tumor, while farther back a crossed bundle of collateral macular fibers would escape. At first it was thought that this crossing took place in the chiasm, but that idea was forsaken for the hypothesis that the crossing occurred in the splenium of the corpus callosum. No degenerations passing through the corpus callosum to either occipital lobe have been satisfactorily demonstrated. The evidence on which this hypothesis is based is thus indirect. Penfield, Evans and MacMillan[12] recently reported cases of amputation of the occipital lobe for tumors in which there was no sparing of the macula when the section was anterior to about the level of the splenium but when it was more posterior typical sparing of the macula was obtained. This suggested to them that a collateral bundle of macular fibers crossing to the other occipital lobe in the splenium had been spared by the sections posterior to this level, while all the macular fibers were interrupted by sections anterior to it.

This hypothesis is not, however, generally accepted. Wilbrand[13] at first expressed the opinion that such a crossed bundle of fibers existed, but later announced that he no longer believed it. Globus and Silverstone[14] reported a case of tumor of the occipital lobe extending up to

11. Bair, H.: The Perimetric Diagnosis of Intracranial Lesions, unpublished data.

12. Penfield, W.; Evans, J. P., and MacMillan, J. A.: Visual Pathways in Man with Particular Reference to Macular Representation, Arch. Neurol. & Psychiat. **33**:816-834 (April) 1935.

13. Wilbrand, H.: Ueber die Organisation der kortikalen Fovea und die Erklärung einiger Erscheinungen aus dem Symptomenkomplex der homonymen Hemianopsie, Ztschr. f. Augenh. **54**:1-10, 1925.

14. Globus, J. H., and Silverstone, S. M.: Diagnostic Value of Defects in Visual Fields and Other Ocular Disturbances Associated with Supratentorial Tumors of the Brain, Arch. Ophth. **14**:325-386 (Sept.) 1935.

and including the corpus callosum in which macular vision was preserved. This seems to indicate that no such fibers cross in the corpus callosum.

Putnam,[15] from studies of the distribution of the macular fibers to the cortex of the occipital lobe, concluded that the extensiveness of this distribution is the principal reason for sparing of the macular field of vision in cases of lesions of the occipital lobe. This explanation, although reasonable, must be considered inadequate if one accepts the results of amputations of the occipital lobe in which all the striated area is apparently removed and yet sparing of the macula persists.[12] Another explanation of sparing of the macula is based on the fact that the macular cortex, unlike the rest of the visual cortex, has a triple blood supply and thus is more likely to escape the associated circulatory disturbance commonly caused by a tumor of the brain.

TABLE 1.—*Histologic Types of 211 Tumors of the Temporal Lobe*

Type of Tumor	Cases	Percentage of Total No.
Spongioblastoma multiforme	82	38.9
Astrocytoma	32	15.2
Cystic glioma	25	11.9
Meningioma	21	10.0
Unclassified gliomas	19	9.0
Oligodendroglioma	12	5.7
Astroblastoma	7	3.3
Hemangioendothelioma	5	2.3
Polar spongioblastoma	3	1.4
Sarcoma	2	0.9
Epidermoid cyst	2	0.9
Sheath neuroma	1	0.5

HISTOLOGIC TYPES

Before the visual disturbances themselves were studied, the 211 tumors of the temporal lobe that comprised the series under consideration were grouped according to their histologic classifications. The resulting groups are shown in table 1. The group of cystic gliomas contains the tumors that were diagnosed only by aspiration of fluid and therefore includes some tumors belonging to the other groups. Otherwise, the list deserves no particular comment except that it agrees with the prevalent opinion that the most common tumor to appear in the temporal lobe is of the type known as spongioblastoma multiforme (glioblastoma multiforme).

15. Putnam, T. J.: Studies on the Central Visual System: IV. The Details of the Organization of the Geniculostriate System in Man, Arch. Neurol. & Psychiat. **16**:683-707 (Dec.) 1926.

DEFECTS OF THE VISUAL FIELDS

Of all the visual disturbances encountered in association with tumors of the temporal lobe, the most important is the defect of the visual field, and this will be considered first. The results of studies of the visual fields in the 211 cases are given in tables 2 and 3.

In table 2, "diagnostically defective" fields exhibited defects that were of value in predicting the presence and location of the lesion. Fields not of diagnostic value included those that exhibited only defects such as unilateral amaurosis, central scotomas, enlarged blindspots and generalized depression and contraction which were not considered characteristic of a particular situation of the lesion.

The white test objects that were employed in the perimetric field studies were routinely of 3 mm. diameter except in a few cases in which the visual perception

TABLE 2.—*Studies of the Visual Fields in 211 Cases of Tumor of the Temporal Lobe*

	Cases	Percentage of Total No.
No visual fields tested	31	14.7
Statement of visual fields	9	4.3
Confrontation (rough) fields:		
Normal or not diagnostic	21	10.0
Diagnostically defective	15	7.1
Perimetric fields only, with white test objects:		
Normal or not diagnostic	7	3.3
Diagnostically defective	17	8.1
Perimetric fields with white and colored test objects:		
Normal or not diagnostic	29	13.7
Diagnostically defective	74	35.1
Perimetric fields with white and colored test objects and 1 meter tangent screen studies:		
Normal or not diagnostic	2	0.9
Diagnostically defective	6	2.8

was so reduced that larger sizes were necessary. The colored test objects were routinely of 5 mm. diameter and included usually red, blue and green in the series of Heidelberg papers. The perimeter employed for most of the cases was of the Ferree-Rand design, of 33 cm. radius, while in cases in which studies were made before the introduction of this instrument a nonself-illuminating perimeter of 28 cm. radius, painted black, was used. In studies in the 1-meter tangent screen a 1 mm. white bead usually was used as a test object. In the perimetric studies no fewer than the twelve principal, and frequently many of the intermediate, meridians of the field were studied. All the visual field studies were either made or supervised by the consulting ophthalmologists.

Table 2 demonstrates the value of careful study of the visual fields in the diagnosis and localization of lesions of the temporal lobe. If the findings in the last two groups in this table, which comprise 111 cases, or more than half the series, are taken as representative of the results of careful study of the visual fields, it is notable that in 80, or 72 per cent, of the cases defects of diagnostic value were found. In only 42 per cent of the group in which rough examination of the fields only was possible were there diagnostic defects, in spite of the fact that

the tumors in this group appeared to be generally farther advanced, in view of the more severe symptoms, than those in the former groups.

Table 3 shows the distribution of the principal types of field defects. The hemianopias include all defects involving most of both the upper and the lower part of a half-field. The quadrantic defects include the fields in which a single quadrant, upper or lower and in one or both eyes, was predominantly affected. Cases are included in which the other quadrant in the same half-field was also affected, but to a definitely less degree. Six cases are not included in which field defects, though of diagnostic value, did not fit the foregoing descriptions. These were defects such as homonymous scotomas and peripheral homonymous contractions of small degree. The percentages recorded in table 3 are those of the total number of cases in this table only, thus representing the relative frequencies of the various types of defects.

It was found that the most common visual field defect encountered in the presence of tumors of the temporal lobe was homonymous hemi-

TABLE 3.—*Incidence of the Principal Types of Visual Field Defects Associated with Tumors of the Temporal Lobe*

	Cases	Percentage
Homonymous hemianopia	66	55.9
Homonymous quadrantic defects:		
Upper	40	33.9
Lower	12	10.2

anopia, either complete or incomplete. This is contrary to Cushing's original finding that quadrantic defects were most frequent. Horrax and Putnam,[16] in examining a larger series of patients, which included those seen by Cushing, arrived at results similar to those presented here. Johnson[17] found that quadrantic defects and other forms of incomplete hemianopia are more often associated with lesions in the temporal lobe than with lesions in any other part of the brain.

The finding of normal fields in many cases is difficult to explain. In part it undoubtedly is the result of insufficient delicacy of studies of the visual fields. Some of the patients with normal fields had larger and apparently more destructive tumors than others with very large field defects. The explanation has been offered that since the geniculocalcarine pathways are next to the partially compressible lateral ventricle, an expanding tumor might not destroy them or interfere with their

16. Horrax, G., and Putnam, T. J.: Distortions of the Visual Fields in Cases of Brain Tumor: The Field Defects and Hallucinations Produced by Tumours of the Occipital Lobe, Brain **55**:499-523 (Dec.) 1932.

17. Johnson, T. H.: Homonymous Hemianopia: Some Practical Points in Its Interpretation, with a Report of Forty-Nine Cases in Which the Lesion in the Brain Was Verified, Tr. Am. Ophth. Soc. **33**:90-113, 1935.

function but merely displace them inward. Variations in the blood supply to this region of the brain might also explain such findings.

We were interested in comparing the defects in the fields associated with tumors of the temporal lobe with those accompanying tumors of the occipital lobe, rather than in studying the defects of the visual fields produced by tumors of the temporal lobe alone. Thus, all the defects of the visual fields caused by tumors affecting any part of the geniculocalcarine fasciculus could be compared. The records of all the patients with tumors of the occipital lobes who were seen before 1937 were examined. The group numbered 45, on 33 of whom perimetric studies had been made. In table 4 the principal types of defects presented by these 33 patients are given. Five patients had normal fields, and 1 had defects of no diagnostic significance.

From comparison of the findings that were associated with the two groups of tumors it is evident: (1) that homonymous hemianopia is the most common field defect associated with both groups of tumors

TABLE 4.—*Incidence of the Principal Types of Visual Field Defects Associated with Tumors of the Occipital Lobe*

	Cases	Percentage
Homonymous hemianopia	25	92.6
Homonymous quadrantic defects:		
Upper	1	3.7
Lower	1	3.7

but appears more frequently in association with the occipital group, and (2) that quadrantic defects are more frequently associated with tumors of the temporal than with those of the occipital lobe. Horrax and Putnam,[16] in a shorter series, found that normal fields are present in only 6 per cent of cases of tumor of the occipital lobe. They stated that this was uncommon with tumors of the occipital lobe but was common with those of the temporal lobe. The figures we obtained do not agree with this, and it is believed that the normality of fields should be disregarded as a sign of any value in distinguishing between the two groups of tumors.

A further comparison was made between the defects of the visual fields produced by the two groups of tumors with regard to the sparing of the macular field of vision. In the group of tumors of the temporal lobe there were sparing of the macula in only 30.5 per cent of the cases in which hemianopic or quadrantic anopia was present and splitting of the macula in the remaining 69.5 per cent. In the occipital group the macular area was spared in 57.1 per cent of the cases and split in 42.9 per cent. Thus, both sparing and splitting of the macula are found in the field defects produced by both groups of tumors, but this series

helps to substantiate the previously existing opinion that sparing of the macula is more common with tumors of the occipital lobe than with those of the temporal lobe.

It should be pointed out that sparing of the macula may represent simply a stage in a progressive field defect which, if allowed to progress, would eventually split the macula. Because of the compact arrangement of the visual fibers in the temporal lobe and their gradual spreading as they extend posteriorly to the occipital lobe, it would be expected that a tumor affecting the portion in the temporal lobe would cause the stage of splitting of the macula to be attained earlier than in the case of a tumor affecting the posterior portions. Consequently, by the time a tumor produces symptoms sufficient to demand medical attention, a field defect with splitting of the macula is more likely to be found in association with tumor in the temporal lobe than in those in the occipital lobe. Its frequency in the former would therefore be greater than in the latter.[18]

The greater relative frequency of quadrantic field defects in cases of tumor of the temporal lobe than in those of tumor of the occipital lobe may be explained by the relative positions of the various groups of visual fibers in these regions. The spread of the fibers in the anterior part of the geniculocalcarine pathway is largely in a lateral direction and gives some degree of segregation of the upper and lower retinal fibers in this direction. The former at first are the more deeply placed

18. A new possibility in the explanation of sparing of the macula will be presented in another publication. Briefly, it rests on the fact that under the usual lighting conditions which prevail in examination of the visual fields, the sensibility for the perception of light differences increases from the periphery to the center of the visual field. Generalized depression of the sensibility over an entire half of the field may be caused by a generalized disturbance, without complete interruption of conduction, of one postchiasmal visual pathway. This may be of a degree great enough to prevent the perception of a given difference in brightness between the test object and the background in the periphery of the field, yet not great enough to prevent this perception in the macular part of the field, where the sensibility is relatively greater than in the periphery. By reducing the brightness of the background to a certain level, it has been found possible to produce a condition of approximately uniform sensibility for a given test object over the central and paracentral parts of the field. When this condition had been produced, splitting of the macula was found in several cases in which there had appeared to be typical sparing of the macula in the ordinary examination. One of these was verified, but the other was a suspected case of lesion of the occipital lobe. This line of investigation is being pursued further, but at present the findings suggest that the apparently spared fibers of the macular field are not completely spared, but are affected to some degree, together with the other fibers from the homonymous half-fields, the appearance of sparing being the result of greater sensibility in the macular region of the field because of the relatively high brightness of the background to which the eye is adapted.

and the more compact and are less exposed to direct disturbance by expanding lesions in the temporal lobe than the latter, which lie more laterally and are more spread out. Thus, most tumors which occupy the body of the temporal lobe would, in their early stages, be more likely to cause greater disturbance of the lower retinal fibers and therefore of the upper visual field quadrants than of the upper retinal fibers and of the lower field quadrants.

In the occipital lobe the fibers representing both upper and lower retinal quadrants are about equally spread out above and below the level of the calcarine fissure and therefore would have about an equal chance of being affected by expanding lesions in this region.

The greater relative frequency of hemianopia in cases of tumor of the occipital lobe than in those of tumor of the temporal lobe is explained most logically by the fact that tumors of the occipital lobe usually do not cause symptoms other than visual disturbances. The patients usually do not become acutely aware of such disturbances until they are advanced or until other, more general symptoms associated with advanced lesions appear. By this time full hemianopias rather than limited peripheral defects are likely to be found. In cases of tumor of the temporal lobe, on the other hand, other aspects of the symptomatology are more frequently the earliest cause of the patient seeking medical attention, and the disturbance of the visual fields is less likely to have progressed to the stage of hemianopia by the time the patient is examined than in cases of tumor of the occipital lobe.

The findings in the visual fields that were associated with the various histologic types of tumors of the temporal lobe were also studied. The tumors listed in table 1 under "unclassified gliomas" have been omitted in this comparison, for each numbers so few cases that the results are of no significance. This study served principally to show that there are no typical findings in the fields that any particular type of tumor can be relied on to produce and that, therefore, findings in the visual fields cannot be used in an attempt to predict what the report of biopsy will be. Of cases in which homonymous hemianopia was found, its occurrence was most frequent in the cystic glioma group. Any tumor that is advanced enough to become cystic is likely also to be large enough to interfere with all the visual fibers passing it and thus to cause a complete hemianopic defect. The highest incidence of the miscellaneous, rather nondescript, types of defect was associated with the group of meningiomas. These tumors are likely to be on the floor of the skull, and although in the cases included here the temporal lobes were affected primarily, the growths may extend forward and compress the tracts, chiasm and even the optic nerves, with the result that bizarre and non-

characteristic field defects are produced. Elsberg [19] also found a high incidence of this type of visual field defect in association with meningiomas.

If a visual field defect is present in a case of tumor of one temporal lobe, it is usually considered to be an absolute indication of the side on which the tumor lies, its lateralizing value outweighing that of all other signs and symptoms. However, as 1 case in this series illustrates, this sign cannot be considered infallible. The hemianopia of 1 patient was on the same side as the tumor. The patient was relieved of his symptoms by operation, and one can do no more than speculate as to what caused such a condition. It is unlikely that there was another, larger tumor on the opposite side of the brain, although a vascular lesion may have been present there. It is less likely that the tumor, in displacing the entire brain toward the other side, had pressed the opposite optic tract against one of the vessels in the circle of Willis.

EXAMINATION OF NECROPSY SPECIMENS

Of all the information pertaining to the defects found in the visual fields, the most worth while was that derived from examination of the necropsy specimens of the brain. Most of the brains preserved in the museum of the Mayo Clinic have been cut into coronal serial sections approximately 1 cm. in thickness. After remaining in formaldehyde, some of them for many years, it is difficult to arrange the sections in the exact form the original brain presented. Because of this distortion, it was thought unwise to attempt any meticulous calculations of the size and shape of the tumors, and the following plan was devised. An extensible rule was constructed, made of a coiled spring with eight markers attached to it at equal distances apart. Marker 1 was placed at the very anterior tip of the temporal lobe, and marker 8, at the posterior tip of the occipital lobe, the brain being then equally divided into several sections. It was found that, regardless of the size or shape of the brain, marker 4 almost invariably was at the level of the lateral geniculate bodies, marker 5 at the very posterior end of the corpus callosum and marker 6 at the dividing line between the temporal and the occipital lobe. The advantage of using this extensible rule was that brains of all sizes could be measured and proportionate measurements readily obtained. Figure 2 shows the scale superimposed on a diagram of the lateral aspect of the brain. The subdivision of the lateral aspect of the lobe into three spaces in a superior-inferior plane was done in a similar manner, the top of the sylvian fissure, where the temporal lobe meets the parietal, being used as the superior point in this measurement and the lowest part of the lobe as the inferior point. By this cross measurement, accurate charting of the tumors could be done in two planes. The charting actually was done in three planes, a drawing of the lateromedial depth of each tumor also being recorded.

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19. Elsberg, C. A.: The Meningeal Fibroblastomas on the Under Surface of the Temporal Lobe, and Their Surgical Treatment, Bull. Neurol. Inst. New York **2**:95-118 (March) 1932.

To continue the comparison of tumors of the occipital and those of the temporal lobe: All the existing specimens of brains containing tumors of the occipital lobe, which numbered 16, were studied, as well as the 52 specimens of tumors of the temporal lobe. The tumors were grouped according to the letters in the spaces, as indicated in figure 2. In most instances the entire tumor could not be included entirely in any one division, but was placed in the group in which the largest mass of the tumor was located.

Of tumors of group *a*, at the anterior end of the temporal lobe, there were 3 specimens. Examination of 1 of the patients with a tumor in this region demonstrated homonymous notching of the upper quadrants of the visual fields. The corresponding tumor was entirely anterior to the level of the lateral geniculate bodies, and there was no evidence of pressure downward on the optic tracts, the tumor being small, entirely

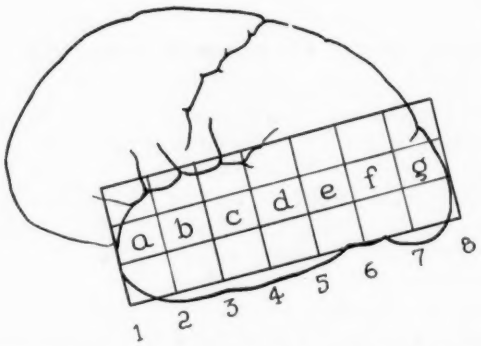

Fig. 2.—Diagram of the lateral aspect of the brain showing the arbitrary subdivision used in studying the situation and extent of the tumors in the necropsy specimens. Line *4* marks the level of the lateral geniculate bodies; line *5* is at the level of the posterior end of the splenium of the corpus callosum, and line *6*, at the separation of the temporal and the occipital lobe.

confined within the lobe and not expanding it. There was no evidence of increased intracranial pressure—no choked disk. This is taken as evidence that the optic radiation can be directly affected at a level anterior to the lateral geniculate bodies, or, in other words, that there is such an anatomic entity as Meyer's loop. This does not agree with the contention of Traquair and McConnell.

In the other 2 cases represented by tumors of group *a*, 1 patient had a field defect that was placed in the miscellaneous type in table 1. This patient was blind in one eye and had irregular, contracted fields in the other. There was marked evidence of pressure on the optic tract. The third patient had no field defect. This tumor was small, in the very tip of the lobe, undoubtedly anterior to the radiations.

Of tumors of group *b* there were 12 specimens. In 3 cases there were homonymous quadrantic defects, more marked than in the cases represented by tumors of group *a*, for in each case the entire quadrant was affected. This was the most common defect found in examination of the 12 patients represented by this group and was taken to be the typical one associated with tumors in this location. There were several interesting features in the 3 cases. In 1 the defects of the visual fields were congruous, and in the other 2 they were incongruous. One of the patients with incongruous defects had a large tumor extending back to the level of the lateral geniculate body at line *4*, but with no evidence of pressure downward on the optic tract. The defect was larger in the field of the eye on the side opposite the tumor. This agrees with the opinion expressed earlier in the paper that incongruous defects might be caused by interference with the beginning of the geniculocalcarine pathway and that one would expect the defect in the field of the contralateral eye to be the larger. This finding is another contradiction to the opinion of Traquair that defects produced by interference with the geniculocalcarine pathway must always be congruous.

The second patient with incongruous defects had the larger defect in the field of the eye on the same side as the tumor, and in this instance there was clear evidence of pressure downward on the optic tract on that side. This agrees also with knowledge of the anatomic relations of the tracts, for the fibers from the ipsilateral eye are placed superiorly and laterally and are in a position to be affected earlier by pressure from above than the corresponding fibers from the opposite eye. Incongruous field defects may be the result, therefore, of interference with the optic pathways anterior to or in the lateral geniculate bodies, or of interference in the anterior part of the geniculocalcarine fasciculus. If the larger defect is in the field of the eye on the same side as the tumor, the interference is more likely to be with the tracts; if the larger defect is in the field of the eye on the other side, the interference is more likely to be with the geniculocalcarine pathway.

Findings in the remainder of the cases of group *b* were as follows: In 1 there was homonymous hemianopia, and in 1, a normal field; in 1 case one eye was removed and there was an enlarged blindspot in the other, and in 6 cases the visual fields could not be tested.

Group *c* represented 18 patients. Three of these had homonymous hemianopia without sparing of the macular field, and 3 had homonymous upper quadrantic defects. These two types of defect were the ones encountered most frequently in association with the tumors of this group and were therefore considered the typical defects for the group. In 2 of the 3 patients with homonymous upper quadrantic anopias, the defects were congruous, and there was no evidence of pressure on the optic

tracts. In the other patient the defects were incongruous, the larger defect being in the eye on the same side as the tumor. In this case there was gross evidence of marked compression of the optic tract. This further substantiates the correlation with the anatomic relations, as previously stated. Of the remainder of the patients who had tumors that were placed in group *c*, 1 had homonymous lower quadrantic anopia associated with a highly placed tumor. Two had normal fields; 6 had fields that appeared normal on rough examination, and 3 were too uncooperative to be examined satisfactorily.

In 2 patients the greatest bulk of the tumor did not fall into any of the lettered groups, but lay directly on line *4*. Both these tumors were laterally placed, away from the optic peduncles, and thus did not help in the study of incongruity of the visual fields. One of the patients had normal fields, and the other had fields that were concentrically contracted, with enlarged blindspots. The optic disks in the latter case were edematous to a degree of from 4 to 5 D., and the field changes were attributable, presumably, to the effects of the increased intracranial pressure and not to interference with any particular part of the optic pathways.

In group *d* 5 cases were represented. In 2 of the cases there was homonymous hemianopia with splitting of the macula, and as this was the most frequent field defect encountered in this group, it was taken as typical for the group. In 1 of the other cases in this group the fields were generally contracted; in another they were normal on rough testing, and in the remaining case they could not be tested.

In all cases of homonymous hemianopia associated with the specimens so far described there was splitting of the macula. In no case was there sparing of the macula. It was thought that if, as the tumors occurred farther and farther posteriorly, full sparing of the macula appeared at a definite level it would be evidence that a bundle of fibers had left the fasciculus and crossed to the other side at this level. On the other hand, if sparing of the macula gradually made its appearance, with more marked sparing as the occipital lobe was approached, it would indicate that no such bundle of crossed fibers existed.

In the next group, group *e*, the tumors were situated at the point of transition between the temporal and the occipital lobe. The findings in the cases represented in this group should be of value, therefore, in deciding whether or not a bundle of crossed collateral macular fibers exists. Unfortunately, the 4 cases in this group were disappointing, as in 1 instance the fields were normal and in the other 3 they could not be tested. Therefore, this series contained no concrete indication either of the presence or of the absence of a bundle of macular fibers crossing in the corpus callosum. It is true that there are several cases in which certain indications were presented, some for and some against the

hypothesis, but the numbers on each side are about equal, and thus they cannot be used as arguments for either side of the question. Attention, however, should be called to the fact that in the group of specimens obtained at necropsy, in which the exact location of the tumor could be determined with a far greater degree of accuracy than in the rest of the 211 cases, there was no instance of sparing of the macula in the case of a tumor lying anterior to the level of the splenium of the corpus callosum. As in these cases in which necropsy was performed the disease obviously was in an advanced stage, this fact should be considered in relation to the statement previously made that sparing of the macula may be only a stage in a progressive field defect that would be more likely to become complete if the associated tumor were in the temporal lobe than if it were in the occipital lobe.

In group *f* 16 cases were represented, in all of which the tumors were in the occipital lobe. The most common field defect was homonymous hemianopia with sparing of the macula; it was present in 5 cases. In 2 cases the sparing amounted to 5 degrees; in 2 other instances it was 10 degrees, and in 1 case the amount was not recorded. Three of the patients who had homonymous hemianopia were subjected to perimetric tests, but the results were not charted; therefore the presence or absence of sparing of the macula could not be determined. One patient had homonymous hemianopia without sparing of the macula. The anterior end of the tumor extended up to line 5. One patient had lower quadrantic anopia, associated with a highly placed tumor. Another patient had normal fields, the tumor in the corresponding specimen being placed too high to interfere with the visual fibers. One patient had normal fields by rough testing; in the 4 remaining instances testing was not possible. No tumors were observed in the part of the brain designated by *g*.

Examination of the specimens obtained at necropsy and correlation of the observations with the fields that the patients had shown were disappointing in that satisfactory evidence for or against a crossing bundle of macular fibers was lacking. However, it was established to our satisfaction that Meyer's loop actually exists and that tumors anterior to the plane of the lateral geniculate bodies may cause field defects by interference with this loop of visual fibers. It was also found that incongruous field defects do not necessarily mean involvement of the optic tract. If the defect is larger in the field of the eye on the side opposite the tumor, the interference with the pathway is probably at the beginning of the geniculocalcarine fasciculus—that is, at the optic peduncle.

It was also learned that in association with tumors in the anterior part of the temporal lobe the most common type of field defect is homonymous quadrantic anopia. With tumors in the middle and posterior

parts of the temporal lobe the most frequent field defect is homonymous hemianopia without sparing of the macula, while with tumors of the occipital lobe the most common form is homonymous hemianopia with sparing of the macula.

VISUAL DISTURBANCES OTHER THAN FIELD DEFECTS

Other visual disturbances were studied to see whether any appeared in a percentage of cases high enough to be of diagnostic or lateralizing value in cases of tumor of the temporal lobe.

Visual Acuity.—With regard to subjective disturbances of visual acuity, 87 of the 211 patients, or 41.2 per cent, stated definitely that there was no impairment of vision. One hundred and six, or 50.2 per cent, stated that there was subjective impairment. In 2 of these it was known that the impairment was the result of causes other than the tumor; in 1 it was attributable to an old ocular injury and in the other to trachoma. In 18 of the cases there was no record of subjective acuity of vision, most of the patients having been brought to the hospital unconscious. Of the 87 patients with subjectively normal vision, there were 5 with objectively defective vision; the defective vision of 4 was attributable to errors in refraction, and that of 1 to corneal opacity. Of the 106 patients with subjectively impaired vision, 34 had objectively normal vision; 15 could not be tested, and the remaining 57 had objective evidence of impaired vision. In the group of 34 patients who had subjectively impaired, but objectively normal, vision, 30 had field defects, the subjective disturbance of vision apparently being caused by the field defects, which were not extensive enough to affect macular visual acuity. On the whole, comparison of the incidence of the subjective and objective loss of visual acuity with the rest of the symptoms offered little of diagnostic value.

Choked Disks.—Gibbs,[20] Martin [21] and Horsley [22] expressed the opinion that a difference in the degree of choked disks in the two eyes has value in the lateralization of tumors of the temporal lobe, the greater amount of choking usually being on the same side as the tumor. Lillie,[23]

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20. Gibbs, F. A.: Intracranial Tumor with Unequal Choked Disk: Relationship Between the Side of Greater Choking and the Position of the Tumor, Arch. Neurol. & Psychiat. **27**:828-835 (April) 1932.

21. Martin, J. M., cited by Gibbs.[20]

22. Horsley, V., in discussion on Paton.[24]

23. Lillie, W. I.: Ocular Phenomena Produced by Temporal Lobe Tumors, J. A. M. A. **85**:1465-1467 (Nov. 7) 1925.

Paton,[24] Kolodny [25] and Schachter [26] expressed the opinion that these differences in the amount of choking are without lateralizing value. Swift [27] stated that the greater amount of choking, when appearing on the side of the tumor, is the result of interference with venous drainage from the optic nerve on that side, because the temporal lobe lies directly over the veins involved.

In 3 of the 211 cases of tumor of the temporal lobe there was no record of examination of the ocular fundi. Of the remaining 208 cases there was no papilledema in 70, or 33.7 per cent, although in 6 of these the patients were reported as having "structurally full disks," and in 82, or 39.4 per cent, there was the same degree of choked disks in the two eyes. In 37, or 17.8 per cent, of the 56 cases in which unequal degrees of choking were found in the two eyes, the greater amount was in the eye on the same side as the tumor, and in 19, or 9.1 per cent, on the side opposite the tumor. In the former group the average difference in the elevations of the disks was 1.08 D., and in the latter, 0.97 D.

All examinations of the ocular fundi were made by experienced ophthalmologists. The degree of choked disk usually was measured to the nearest diopter of elevation, measurements that seemed to fall between definite units, as indicated on the records, being taken as of half-diopter values for the statistical purposes of this study. In instances of obvious low grade or early papilledema in which no elevation of the disk was measurable, values were also expressed in half-diopters. In all cases in which operation was performed only the fundic findings just before the first operation were considered.

The tumors in the 211 cases were about equally divided between the right and the left side of the brain, 101 being on the right and 110 on the left. Of the 152 cases in which either there was no choked disk or the choking in the two eyes was of the same degree, the tumor was on the right in 75 and on the left in 77. Of the cases in which there was no choked disk, the tumor was on the right in 30 and on the left in 40. Of the cases in which the degree of choking of the disk was the same in the two eyes, the tumor was on the right in 45 and on the left in 37. Therefore, the side of the brain on which the tumor was located apparently had no bearing on the presence or absence of choked disk or on the equality or inequality of the degree of papilledema in the two eyes.

24. Paton, L.: Optic Neuritis in Cerebral Tumours, Tr. Ophth. Soc. U. Kingdom **28**:112-144, 1908.

25. Kolodny, A.: The Symptomatology of Tumours of the Temporal Lobe, Brain **51**:385-417 (Oct.) 1928.

26. Schachter, M.: Les tumeurs du lobe temporal; leur aspect clinique, Paris méd. **2**:229-231 (Sept. 24) 1932.

27. Swift, G. W.: Choked Disc in Intracranial Lesions: The Mechanical Factor in Its Causation, Northwest Med. **26**:579-585 (Dec.) 1927.

Of the 37 cases in which the tumor and the greater degree of choked disk were on the same side, the tumor was on the right in 17 and on the left in 20. Of the cases in which the greater choking of the disk was contralateral to the tumor, the tumor was on the right in 9 and on the left in 10. Thus, whether the greater choking appeared on the same side as the tumor or on the opposite side, it bore no relation to the side of the brain on which the tumor occurred. It therefore appears logical to conclude that the almost twofold incidence of ipsilateral as compared with contralateral choked disk is not due to any physiologic or anatomic factors, but is the result primarily of the presence of the tumor. The mechanism of the production of inequality of choked disks is open to speculation, although differences of intraocular tension in the two eyes and greater venous congestion and edema of the brain on the side of the tumor probably are fundamental factors. In spite of the probability, however, that a tumor is on the side of the greater choked disk, the possibility that in approximately 34 per cent of instances of inequality of choked disks the tumor may be on the side opposite the greater choked disk makes this criterion of lateralization clinically unreliable as compared with the much greater reliability of other lateralizing signs, such as homonymous field defects and unilateral positive neurologic signs. For this reason, we believe that a difference in the degree of choking of the disks in the two eyes is of no definite clinical value as a lateralizing sign.

Equality of the Pupils.—In some of the earlier attempts of German authors to formulate the symptomatology of this group of tumors, changes in pupillary size were stressed. Behr [28] said that any tumor pressing on the optic tract causes dilatation of the opposite pupil. Of the present group, in only 37 cases, or 17.5 per cent, was there inequality in size of the pupils. The estimations were made by gross comparison, and not by pupillometric readings. Of these, in 18 cases the larger pupil was on the side of the tumor, and in 19 it was on the opposite side. Thus, there was no correlation with the lateral position of the tumor.

Reaction of Pupils.—Similar claims have been made for disturbance in pupillary reaction. Kennedy [29] stated that a fluctuating Argyll Robertson pupil may be expected. Of the 211 patients, the pupillary reactions were normal except in 33, or 15.6 per cent. Testing was done routinely with the use of a hand flashlight. Of the 33 patients, 14 had

28. Behr, K.: Die Bedeutung der Pupillenstörungen für die Herddiagnose der homonymen Hemianopsie und ihre Beziehungen zur Theorie der Pupillenbewegung, Deutsche Ztschr. f. Nervenh. **46**:88-108 (Dec.) 1912.

29. Kennedy, F.: Symptomatology and Diagnosis of Expanding Lesions of the Brain, with Special Reference to Disturbances of Vision, Hearing, Taste, Smell and Speech, Tr. Am. Acad. Ophth., 1925, pp. 8-25.

pupillary reactions that were markedly diminished, the light and the convergence-accommodation reactions being about equally affected. The remaining 19 patients had disturbances suggestive of the Argyll Robertson type, with the light reaction reduced more than the convergence-accommodation reaction or the latter not at all. In 20 of the 33 cases, the reduction of pupillary reaction was approximately of the same degree in each eye. In 10 of the remaining 13 cases in which the pupillary reaction was unequal, the reduction in reaction was more marked in the eye opposite the tumor and in 3, more marked on the same side. Two of these 3 patients had meningiomas on the floor of the middle fossa. This may be of some significance, the disturbance in pupillary reaction in the latter cases being caused by pressure on the third cranial nerve on that side, while the other unequal reactions were caused by a more centrally placed disturbance which was crossed in its effect.

Ptosis.—Ptosis was present in only 10, or 4.7 per cent, of the cases; in 1 of these it had been present for many years and was not related to the tumor. Of the remaining 9 cases, the ptosis was present on the side of the tumor in 5 and on the opposite side in 4. Thus, ptosis apparently is of no lateralizing value.

Ocular Movements.—Only 25 of the patients, or 11.8 per cent, showed any disturbance of the movements of the eyes. One had impairment of upward gaze; another had weakness of convergence and weakness of the left lateral rectus muscle associated with a tumor of the left side. One had impairment of the left third cranial nerve, which also was associated with a tumor on the same side. In 6 cases there was impairment of convergence only. Two other patients had bilateral involvement of the sixth cranial nerve. Fourteen patients had unilateral weakness of the external rectus muscle. Of these, the weakness of the external rectus muscle was on the side of the tumor in 7 cases and on the opposite side in 7. Thus, this sign cannot be used to lateralize the tumor.

Diplopia.—Diplopia was either complained of or demonstrated in 43, or 20.4 per cent, of the 211 patients.

Nystagmus.—An appreciable degree of nystagmus was present in 20, or 9.5 per cent, of the cases. In 15 of these the nystagmus was of the horizontal type; in 3, both vertical and horizontal; in 1, vertical only, and in 1, rotary. The relation of nystagmus to other vestibular signs and to the whole group of manifestations called "pseudocerebellar signs" that are found in cases of tumor of the temporal lobe will be considered in a subsequent publication.

Visual Hallucinations.—The visual hallucinations sometimes produced by tumors of the temporal lobe have provoked considerable discussion. It seems now to be generally agreed that disturbances in the temporal

lobe are more likely to produce formed hallucinations, actual objects such as persons and animals, while those in the occipital lobe are more likely to cause unformed hallucinations, such as whirling lights and colors. This difference has come to be used as a differential point in the diagnosis.

In the present group of 211 patients, 22 or 10.4 per cent, had visual hallucinations. Of these, 11 had unformed and 11 formed hallucinations. Among the objects seen by the patients with formed hallucinations were faces in soap bubbles rising to the ceiling, rats, flies, ants, a steer's head and a striped blanket with a human figure on it. In only 2 cases were the images seen in a blind half of the visual field. The rest of the images appeared in the seeing half of the field or oscillated back and forth from the seeing to the blind part of the field. In 2 other cases there were no actual hallucinations, but there were present experiences that may be somewhat related to hallucinations. One of these 2 patients said that her "mother once looked funny, like an old picture." The other volunteered the information that objects seemed to persist long after changing the glance.

The number of instances of visual hallucinations occurring with tumors of the occipital lobe was compared with that associated with tumors of the temporal lobe. Of the 45 patients with tumors in the occipital region, 4, or 8.9 per cent, had visual hallucinations, and here again the numbers of formed and of unformed hallucinations were equal, there having been 2 of each kind. Of course, these numbers are too small to be regarded seriously, but they do not substantiate the belief that formed hallucinations arise chiefly from disturbances of the temporal lobe and unformed hallucinations chiefly from disturbances of the occipital lobe.

SUMMARY AND CONCLUSIONS

1. Homonymous hemianopia is the most common visual field defect produced by tumors of the temporal and occipital lobes.

2. Quadrantic anopias are produced much more frequently by tumors of the temporal lobe than by tumors of the occipital lobe.

3. Normal fields occur with approximately the same frequency in cases of tumor of the temporal lobe and in cases of tumor of the occipital lobe.

4. Sparing of the macula occurs in association with both groups of tumors, but is much more common and of greater degree with the group of tumors of the occipital lobe. In the cases in which necropsy specimens were available there was no instance of sparing of the macula associated with a tumor of the temporal lobe.

5. There is definite evidence in the study of this group of tumors to indicate that the forward looping of the geniculocalcarine fasciculus, as described by Meyer, actually exists. Lesions which affect this portion of the fasciculus may produce a typical picture of the visual fields which is of diagnostic value.

6. Incongruous homonymous field defects can be produced by tumors of the temporal lobe which affect either the lateral aspect of the homolateral optic tract or the beginning of the geniculocalcarine fasciculus. In the former case the larger defect is in the field of the homolateral eye; in the latter, in the field of the contralateral eye.

7. No concrete evidence was obtained either for or against the presence of a crossing bundle of fibers to allow representation of each half of the retinal macula in both occipital lobes.

8. The presence or absence of choked disks and the equality or inequality of the degree of choking in the two eyes are of no clinical value in deciding on which side of the brain a tumor of the temporal lobe is located. Although with unequal degrees of choking of the disks in the two eyes there is more likelihood of the tumor being on the side of the greater choking than on the opposite side, this criterion is too unreliable to be of any value in lateralization of the tumor.

9. Visual disturbances other than the field defects are of no value in helping to diagnose or lateralize tumors of the temporal lobe.

VASCULAR PATTERN OF CERTAIN INTRACRANIAL NEOPLASMS

STUDIES WITH THE BENZIDINE STAIN

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This study was conducted for the purpose of determining the vascular pattern of a group of tumors of the brain. Numerous pathologic reports and classifications of intracranial neoplasms appear in the literature, with an occasional investigator devoting particular attention to the vascular arrangement. Elsberg and Hare [1] determined the number and situation of vessels in tumors of the brain as seen in ordinary stained specimens. Special stains, such as the Perdrau ammoniacal silver method for the study of reticulin around blood vessels, have been used.[2] Articles have been devoted to the special study of changes in the blood vessels of gliomas, particularly spongioblastoma multiforme.[3] Campbell, Alexander and Putnam [4] applied the technic of the benzidine stain to the study of the vascular pattern of a meningioma, while Alexander and Putnam [5] later demonstrated the pattern of an oligodendroglioma and a protoplasmic astrocytoma.

MATERIAL AND METHODS

Most of the pathologic material for this study was obtained in cases of tumor of the brain in which autopsy had been performed. In a few instances biopsy material or surgical specimens were utilized. The tissues were allowed to fix

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1. Elsberg, C. A., and Hare, C. C.: Blood Supply of the Gliomas, Bull. Neurol. Inst. New York **2**:210, 1932.

2. Bailey, P.: Histologic Atlas of Gliomas, Arch. Path. **4**:871 (Dec.) 1927.

3. Deery, E. M.: Some Features of Glioblastoma Multiforme, Bull. Neurol. Inst. New York **2**:157, 1932.

4. Campbell, A. C. P.; Alexander, L., and Putnam, T. J.: Vascular Pattern in Various Lesions of the Human Central Nervous System, Arch. Neurol. & Psychiat. **39**:1150 (June) 1938.

5. Alexander, L., and Putnam, T. J.: Pathologic Alterations of Cerebral Vasculâr Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**:471, 1938.

for one week in 10 per cent solution of formaldehyde. Specimens were then taken from various parts of the neoplasm, and frozen sections 200 microns thick were cut from these blocks, the remainder of the specimen being used for routine histologic stains. The frozen sections were stained with the benzidine technic (Campbell, Alexander and Putnam [4]), while the routine stains were utilized for diagnosis of the neoplasms as well as confirmation of the results of the benzidine stain.

OBSERVATIONS AND RESULTS

MENINGIOMAS

Penfield [6] stated that the blood supply of a meningioma enters the tumor at its dural attachment, the larger vessels passing about the tumor in the capsule. Degeneration, when it occurs, usually takes place in the center, the zone most widely removed from the peripheral blood supply. Freeman [7] stated that the blood vessels are variable in size and number and are often contorted, and have a fairly prominent part in the architecture of the tumor. Biggart [8] noted that in some types of meningiomas the blood vessels constitute the only stroma. Bailey and Bucy [9] stated that the mesenchymal type has numerous small blood vessels with delicate walls, the angioblastic type very abundant blood vessels, the meningotheliomatous type a thick, exceedingly vascular stroma and the psammomatous type an arrangement of whorls, with vessels interspersed between the whorls. Bailey, Cushing and Eisenhardt [10] noted that ordinary meningiomas are notable for their excessive extraneoplastic vascularity. On histologic examination a few of these tumors show an excessive intraneoplastic vascularity; so they are sometimes spoken of as angioendotheliomas. Penfield [11] stated that meningeal fibroblastomas possess a distinct stroma, which is continuous with the dura mater and contains blood vessels derived from the dura. Whorls may have as their center a collagen fiber or a small blood vessel, or

6. Penfield, W.: Tumors of the Sheaths of the Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 953-990.

7. Freeman, W.: Neuropathology, Philadelphia, W. B. Saunders Company, 1933, pp. 302-325.

8. Biggart, J. H.: Pathology of the Nervous System, Baltimore, William Wood & Company, 1936, pp. 255-315.

9. Bailey, P., and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, Am. J. Cancer **15**:15, 1931.

10. Bailey, P.; Cushing, H., and Eisenhardt, L.: Angioblastic Meningiomas, Arch. Path. **6**:953 (Dec.) 1928.

11. Penfield, W.: The Encapsulated Tumors of the Nervous System: Meningeal Fibroblastoma, Perineurial Fibroblastoma and Neurofibromata of von Recklinghausen, Surg., Gynec. & Obst. **45**:178, 1927.

Fig. 1 (case 2).—Photomicrograph (× 15) of the central part of a meningioma, meningotheliomatous type. Benzidine stain. Note the interstitial arrangement of the major vessels, while vessels of finer caliber are seen within the whorls.

Fig. 2 (case 2).—Photomicrograph (× 80) from the central part of a meningioma, meningotheliomatous type. Benzidine stain. Note the vessels hugging the outer circumference of the nodular whorls, which is especially well shown in the nodule above the center of the figure.

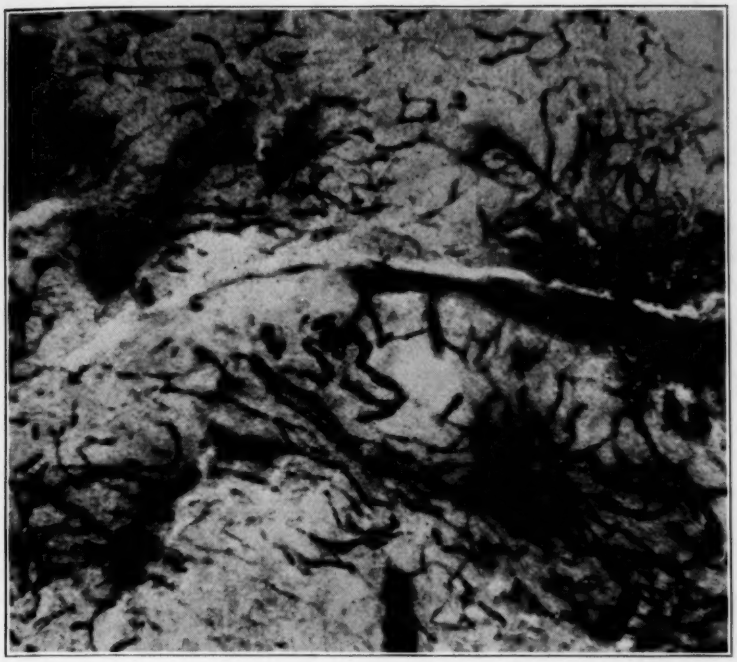

Fig. 3 (case 3).—Photomicrograph (× 55) of a meningioma, meningotheliomatous type. Benzidine stain.

Fig. 4 (case 5).—Photomicrograph (× 190) of a meningioma, psammomatous type. Benzidine stain. Note the psammoma body, slightly to the right of the center of the figure, adjacent to a blood vessel and containing a central core stained black with benzidine, presumably the ferruginous residue of an obliterated blood vessel.

there may be nothing discoverable. Cushing and Eisenhardt [12] described their meningothelial tumors as showing moderate to abundant vascularity.

CASE 1.—*Meningioma, meningotheliomatous type.*

This tumor, measuring 9 by 6 by 4 cm., arose from the orbital portion of the left frontal bone and compressed the corresponding frontal lobe.

Histologic Observations.—Sections from the depth of the neoplasm showed a characteristic meningioma, very cellular, with numerous whorls, some of which contained small blood vessels in their centers. Fairly large, thin-walled vessels were observed between the whorls. Benzidine stains showed irregular sinusoids having a wide-meshed arrangement. The sinusoids measured up to 175 microns in diameter, the average size being 80 microns. The small vessels located within the whorls averaged 20 microns in size.

CASE 2.—*Meningioma, meningotheliomatous type.*

This neoplasm, measuring 2.5 cm. in diameter, was situated on the left sphenoidal ridge and compressed the left temporal lobe.

Histologic Observations.—Stained sections revealed that the tumor was moderately cellular, with numerous whorls. Blood vessels were not conspicuous within the substance of the neoplasm, only an occasional sinusoid being seen. Large vascular sinuses could be seen at the circumference of the tumor, however, Benzidine stains showed the capsule to be the most vascular portion of the tumor, this region containing parallel and interlacing bundles of vessels, the average diameter of which was 75 microns. Within the substance of the tumor most of the vascular supply was located in the tissues about the whorls (fig. 1), usually hugging the circumference of the whorls closely (fig. 2). These vessels averaged 25 microns in size. The vessels which entered the whorls were much smaller, as described in case 1.

CASE 3.—*Meningioma, meningotheliomatous type.*

This specimen was meningioma, measuring 5 by 4 by 4 cm., arising from the left sphenoidal ridge and displacing the overlying left frontal and temporal lobes.

Histologic Observations.—Stained sections revealed an extremely cellular neoplasm, the predominant arrangement being very small whorls, many of them containing only a few cells in each cross section. This tumor was much more vascular than those in the 2 preceding cases. The margin of the neoplasm at its point of compression of cerebral tissue possessed a rich vascular supply, many large vessels being seen. In the depth of the tumor numerous small vessels were located around as well as in the centers of the abundant whorl formations. Benzidine stains (fig. 3) showed a rather vascular tumor in which the numerous sinusoids were arranged in a much closer network than in the other 2 tumors (cases 1 and 2).

CASE 4.—*Meningioma, meningotheliomatous type.*

This tumor was an operative specimen, measuring 5 by 5 by 4 cm., taken from a neoplasm along with the overlying parietal bone, which had been invaded by the growth.

Histologic Observations.—Stained sections showed a cellular neoplasm. Whorl formations were common in the depth of the tumor, and vessels in this area were

12. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C. Thomas, Publisher, 1938, pp. 30-55.

infrequent. The portion of the tumor adjacent to and invading the bone was seen to be much more vascular, a number of closely grouped channels being evident. Benzidine stains from the depth of the tumor showed irregular sinusoidal channels, measuring from 15 to 30 microns in diameter, rather sparsely scattered through the sections and resembling in general the configurations seen in case 2. The portion of the neoplasm invading bone, however, consisted of a number of closely grouped vascular channels, giving the sections the appearance of large pools of blood.

CASE 5.—*Meningioma, psammomatous type.*

This specimen, obtained at operation, was a well encapsulated tumor, measuring 7 by 5 by 5 cm., located in the parasagittal region of the right parietal lobe.

Histologic Observations.—The tumor was moderately cellular, appearing relatively avascular and containing numerous psammoma bodies. Benzidine stains revealed the capsule to be extremely rich in sinusoidal blood vessels, some of which measured up to 150 microns in diameter and showed irregularity of contour. The vascular arrangement within the tumor was similar to that noted in case 2, the larger vessels averaging 75 microns in diameter and being located in the interstices between the whorls. It was interesting to note that the psammoma bodies were clearly visible in these preparations (fig. 4), an occasional psammoma body containing a central core which stained black with benzidine, presumably the ferruginous residue of an obliterated blood vessel. Most of the psammoma bodies, however, did not contain such cores, nor did they show any other relation to blood vessels.

GLIOMAS

MEDULLOBLASTOMA.—Elsberg and Hare [1] stated that in the medulloblastomas the largest number of vessels are present in the central part of the growth. Bailey [2] reported that there are often numerous capillaries in the tumors, with sprouts of reticular tissue passing between the capillaries. Freeman [7] mentioned that these tumors are very vascular and are less prone to degenerative changes than the medulloepitheliomas. According to Biggart,[8] the medulloblastomas are fleshy, hemorrhage or necrosis being unusual. Bailey and Cushing [13] stated that this tumor has numerous small vascular channels. In another communication the same authors [14] stated that in 1 case the blood vessels were large but not numerous, in another there were rather numerous, thin-walled blood vessels and in a third the connective tissue was confined to the walls of the rather rare blood vessels.

CASE 6.—*Medulloblastoma.*

This specimen constituted a portion of a tumor from the cerebellar vermis, removed at operation.

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13. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

14. Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, Arch. Neurol. & Psychiat. **14**:192 (Aug.) 1925.

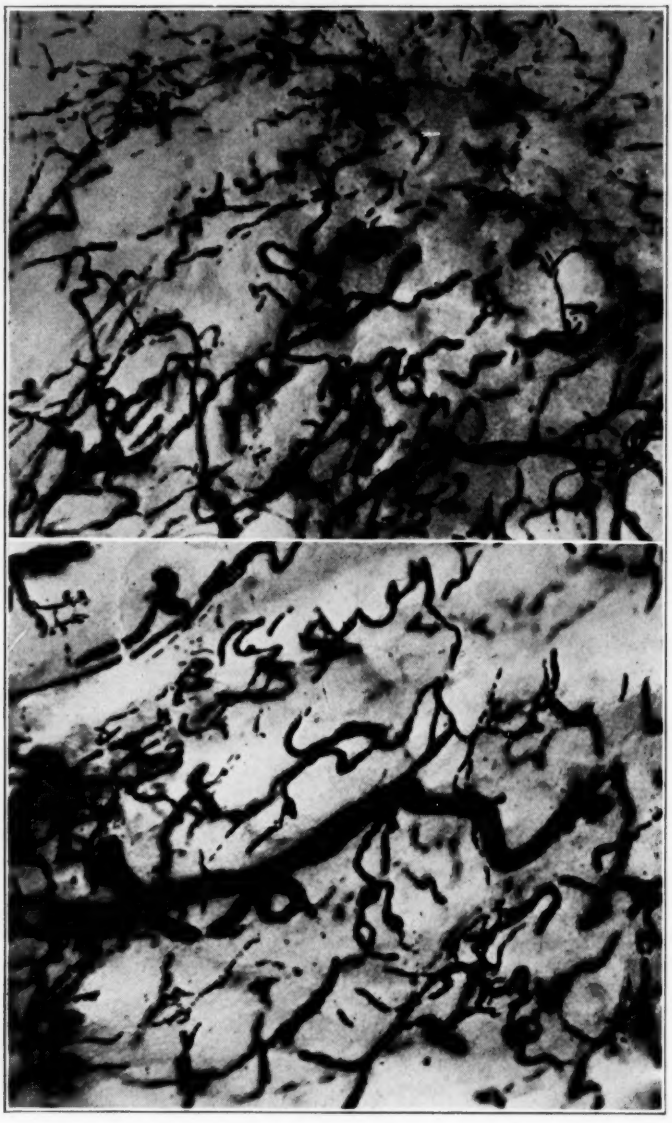

Fig. 5 (case 6).—Photomicrograph (× 55) of a medulloblastoma. Benzidine stain. Note the predominantly interstitial arrangement of sinusoids of rather uniform size, with frequent loop formations.

Histologic Observations.—The neoplasm proved to be highly cellular, with numerous mitotic figures. The stroma was relatively sparse in most places and absent in others. Here and there small blood vessels could be seen coursing through the stroma. Benzidine stains (fig. 5) showed the vessels to be located principally in the interstices between the masses of tumor cells. These vessels averaged 16 microns in size, the sections being rather uniformly vascularized. A great deal of tortuosity, with loop formation and occasional bulbous dilatation, was present. There were occasional vessels of capillary size, measuring 8 microns in width; these vessels apparently followed the edges of the nodular masses, rather than penetrating them.

MEDULLOEPITHELIOMA.—Freeman [7] stated that neoplasms of this type are soft and vascular.

CASE 7.—*Medulloepithelioma.*

A grayish tumor, 5 by 4 by 3 cm., located in the right cerebellar hemisphere, was observed at autopsy.

Histologic Observations.—This specimen was very cellular and had a nodular arrangement (fig. 6). Some of the nodules were extremely cellular, containing practically no stroma and having nuclei with dense chromatin structure and occasional mitotic figures. There was further accumulation of cells along the edges of these nodules. Other zones were less rich in cells, the nuclei of which had a lighter chromatin structure; a fine stroma containing the relatively few blood vessels completed the framework of these zones. The distribution of cells within the nodules of the second type was rather uniform. Benzidine stains (fig. 7) showed an interesting distribution of vessels. The cellular nodules were almost completely devoid of blood vessels, most of the vascular supply being seen in the interstices around the edges of these highly cellular zones. They hugged the margins closely and averaged 16 microns in diameter. Somewhat smaller vessels were distributed in the stroma of the less cellular nodules.

SPONGIOBLASTOMA MULTIFORME.—Elsberg and Hare [1] reported that in the central part of the neoplasm the vessels are few or are not to be seen and that this part is often degenerated. In the white matter, which appears on gross inspection to be adjacent to the margins of the growth and in the periphery of the growth itself, groups of large vessels are almost regularly seen. Deery [3] discussed the peculiar vascular reaction in these tumors. He expressed the belief that necrosis, so common in glioblastoma multiforme, probably is caused as much by focal toxic factors as by decrease in blood supply. Biggart [8] stated that overgrowth of the vascular endothelium is so marked as to occlude the vascular lumen and probably explains the tendency of these tumors to

show necrosis. Bailey and Cushing [13] stated that the vascular sinuses, which vary greatly in number in different tumors, are usually thin walled and show many pathologic changes, such as overgrowth of the adventitia, proliferation of the endothelium and hyaline degeneration of the walls of the vessels. Occlusion of the lumen and necrosis of

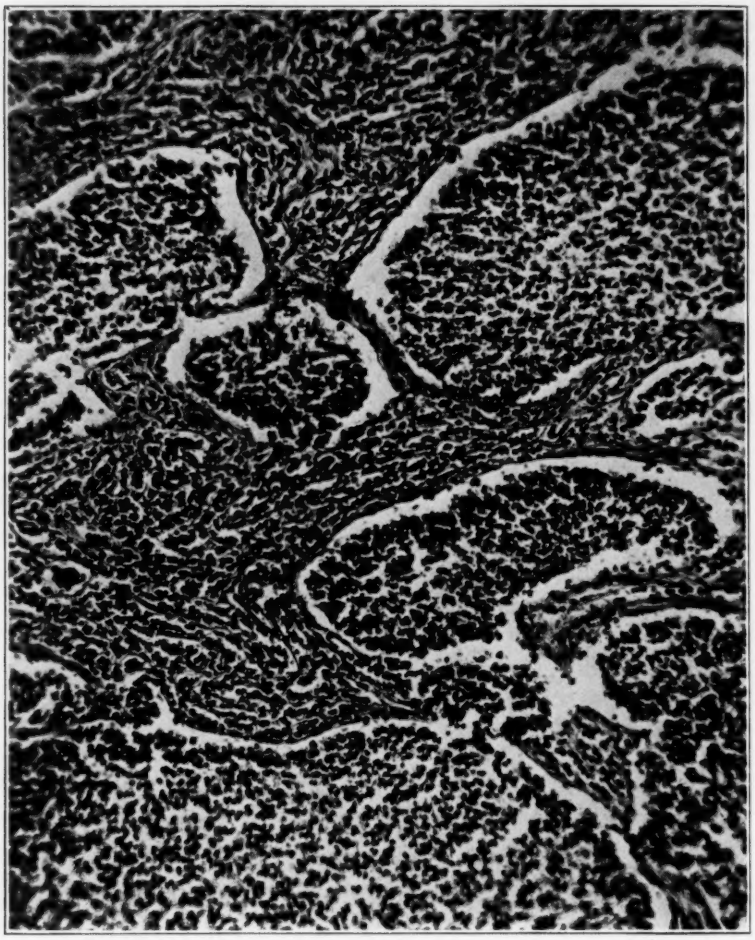

Fig. 6 (case 7).—Photomicrograph (about × 106) of a medulloepithelioma. Hematoxylin and eosin stain. Compare with the benzidine preparation shown in figure 7.

adjacent areas also occur. The fragile and diseased vascular walls, moreover, are easily ruptured, giving rise to extensive hemorrhages. Buckley [15] described similar lesions in his cases of spongioblastoma

15. Buckley, R. C.: Pontile Gliomas: A Pathologic Study and Classification of Twenty-Five Cases, Arch. Path. **9**:779 (April) 1930.

Fig. 7 (case 7).—Photomicrograph (about × 78) of a medulloepithelioma. Benzidine stain. Compare with the preparation stained with hematoxylin and eosin shown in figure 6.

multiforme. Globus and Strauss [16] reported that these neoplasms show intense vascularity, marked destructive properties, large hemorrhagic foci and cystic degenerative changes.

CASE 8.—*Spongioblastoma multiforme.*

This specimen obtained at autopsy, was a large, intensely vascular neoplasm involving practically all the white matter of the right hemisphere.

Histologic Observations.—Stained specimens revealed a highly cellular neoplasm consisting of a multiplicity of types, including giant cells, large astrocytes and spongioblasts. Mitotic figures were abundant. This tumor was vascular and hemorrhagic, hyperplastic changes in vessels being conspicuous. Thrombus formation and recanalization were evident in a number of places. Benzidine specimens (fig. 8) showed striking vascularity, large and small vessels being closely packed together. The largest vessels measured as much as 300 microns in width, the smallest 8 microns. Beading and irregularities of contour, such as corkscrew formations, were common. The pathologic vessels at the margin of the tumor were continuous with the vessels of the neighboring brain tissue. At the periphery of the tumor vascular loops and knots could be seen. Areas of hemorrhage were numerous.

CASE 9.—*Spongioblastoma multiforme.*

In this instance a mass 3 by 2 by 2 cm. involved the dorsal aspect of the pons and medulla. The tumor was firm at the periphery, but the center contained numerous areas of necrosis and hemorrhage.

Histologic Observations.—This neoplasm was very cellular, with a moderate amount of stroma. It was multiform in appearance, showing palisades of spongioblasts, astrocytes and giant cells. Mitoses were frequent. Hyperplastic phenomena were numerous in the vessels, some of which contained well organized or canalized thrombi. Numerous hemorrhagic areas were to be seen. Benzidine stains showed a highly vascular neoplasm, the vascular channels of which measured up to 250 microns in diameter. Irregular variations in caliber, bizarre formations and hemorrhages were common.

POLAR SPONGIOBLASTOMA.—Bailey [17] reported that these tumors are firm, whitish growths, showing little degenerative changes. They are poorly vascularized. Hemorrhages into their substance are infrequent. Hassin [18] stated that these tumors are avascular and solid new growths.

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16. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme, a Primary Malignant Form of Brain Neoplasm: Its Clinical and Anatomic Features, Arch Neurol. & Psychiat. **14**:139 (Aug.) 1925.

17. Bailey, P.: Primary Tumors of the Brain, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, pp. 903-951.

18. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933, pp. 393-434.

CASE 10.—*Polar spongioblastoma.*

This operative specimen was obtained from the left temporal lobe.

Histologic Observations.—Sections showed a cellular tumor with elongated nuclei and slender processes, the arrangement of the cells in palisades and "braids"

Fig. 8 (case 8).—Photomicrograph (× 55) of a spongioblastoma multiforme. Benzidine stain.

being marked. Vessels were infrequently seen in these preparations. Benzidine stains (fig. 9) revealed a sinusoidal network, measuring up to 30 microns in diameter. The largest sinusoids showed a great amount of beading and irregularity, with loop formations. The smallest vessels measured 8 microns in diameter. Characteristic patterns were "shrub" and "wind-swept tree" formations (fig. 9), somewhat reminiscent of the "palisades" and "braids" of the cellular arrangement.

CASE 11.—*Polar spongioblastoma.*

Autopsy in this case showed a tumor, measuring 4 cm. in diameter, in the right occipital lobe. A second tumor, measuring 1.5 cm. in diameter, was observed in the superior parietal lobule on the right.

Fig. 9 (case 10).—Photomicrograph (× 32) of a polar spongioblastoma. Benzidine stain. Note the "shrub" and "wind-swept tree" formations.

Histologic Observations.—This was a very cellular neoplasm, consisting of parallel rows of spongioblasts arranged in palisades. The tumor was very vascular, there being necrosis in some portions of the neoplasm. A few of the vessels showed adventitial proliferation. The vascular network, as demonstrated by

benzidine preparations, consisted of middle-sized sinusoids, measuring 20 to 30 microns in diameter, occasionally arranged in interlacing bizarre patterns, including "shrub" and "wind-swept tree" formations. In other areas they formed a wide-meshed network, having occasional beadlike irregularities and rete mirabile formations.

CASE 12.—*Polar spongioblastoma.*

This tumor measured 2.5 by 2 by 2 cm. and involved the pons and medulla.

Histologic Observations.—The neoplasm was moderately cellular, with oval and elongated nuclei and spindle-shaped cells. Mitotic figures were fairly numerous. The tumor appeared vascular in these preparations. The vascular pattern, as shown by the benzidine stain, consisted of moderately numerous, irregular channels, measuring up to 50 microns in diameter, with "tree" formations similar to those seen in cases 10 and 11.

CASE 13.—*Spongioblastic hamartomatous malformation.*

This specimen was obtained from a stillborn child, whose brain showed no gross lesions at autopsy except a slight degree of vascular congestion in the periventricular region.

Histologic Examination.—The subependymal region of the left lateral ventricle was involved by fairly vascular gliomatous tissue, containing cells with round, oval and elongated nuclei. The oval type predominated and was especially dense about the vena striae terminalis. Polar spongioblasts with an admixture of astrocytes and a scant amount of cytoplasm constituted the bulk of this tumor. There was a well defined glial reticulum. Mitotic figures were not seen. Benzidine stains revealed this neoplastic formation to be supplied with variably sized vessels, several large ones measuring 350 microns in diameter and the small ones averaging 10 microns. These vessels formed a dense, interlacing, shrublike network, similar to that of the polar spongioblastomas.

ASTROBLASTOMA.—Bailey [17] noted fewer hemorrhagic foci in tumors of this type than in the spongioblastoma multiforme. He described radiation of cells around numerous vessels with hypertrophied walls and often extensive intervascular degeneration. Freeman [7] noted the palisading around blood vessels, the vessels being well formed and necrosis unusual. Biggart [8] reported that small areas of necrosis are frequent. There is often a curious overgrowth of blood vessels. Buckley [15] described the astroblastoma as a soft tumor with many areas of necrosis, hemorrhage and cyst formation. Hassin [18] stated that it is rich in blood vessels, around which the cells of the neoplasm are grouped. Bailey and Bucy,[19] in reporting a group of cases, noted that

19. Bailey, P., and Bucy, P. C.: Astroblastomas of the Brain, Acta psychiat. et neurol. **5**:439, 1930.

hemorrhagic areas are not nearly so common in this tumor as in the glioblastoma multiforme. Cystic cavities, however, are frequent. There is an abundance of blood vessels, which are usually isolated one from another and have hypertrophied walls. The intima is only occasionally proliferated. There is a tendency to intervascular degeneration, which leaves a cuff of viable cells around the vessels.

Fig. 10 (case 14).—Photomicrograph (× 42) of an astroblastoma. Benzidine stain.

CASE 14.—*Astroblastoma.*

Autopsy in this case showed a large, infiltrating tumor involving the floor of the third ventricle and invading both thalami. It contained several cysts and areas of necrosis.

Histologic Observations.—Stained sections showed a cellular neoplasm, with a moderate amount of stroma. Palisade arrangement around blood vessels and the presence of well defined sucker feet were conspicuous. There was evidence of considerable necrosis. Hyperplastic changes in the walls of vessels, with thrombosis and recanalization, were in evidence. Benzidine stains showed that

the vessels varied in size from 16 to 400 microns (fig. 10). Outstanding was the wide-meshed network of large sinusoids, many of which were beaded and irregular. In the necrotic zones still more irregularity and beading were noted.

ASTROCYTOMA.—Elsberg and Hare [1] stated that the largest number of vessels occur in the central part of the growth. Bailey [17] reported that blood vessels are rare and are often calcified, especially in the fibrillary type. Freeman [7] stated that the vascular organization of the astrocytomas is such that hemorrhage and necrosis are infrequent. According to Biggart,[8] this tumor is not richly vascular, so that hemorrhages and necrotic areas are not usual features. Bailey and Cushing [13] stated that a protoplasmic astrocytoma is a soft, relatively avascular tumor, almost as liable to degenerative and cystic changes as the spongioblastoma multiforme. The fibrillary astrocytoma, on the other hand, shows a few small blood vessels, and it may be due to this phenomenon that the tumor is prone to cystic degeneration.

CASE 15.—*Protoplasmic astrocytoma.*

This specimen, previously studied by Alexander and Putnam,[5] was a slowly growing invasive tumor involving the left parietal lobe, which measured 5 by 3 by 4 cm. and had given rise to disturbances for five years before the death of the patient.

Histologic Observations.—The tumor was moderately cellular, with a considerable amount of stroma. The tumor cells were typical protoplasmic astrocytes. Their nuclei were uniformly round and contained a dense amount of chromatin material. There were no mitotic figures and no multinucleated giant cells. The cell bodies were large, measuring 12 to 20 microns, and showed a homogeneously hyaline appearance when stained with hematoxylin and eosin or phosphotungstic acid hematoxylin. They all showed fairly numerous astrocytic processes, the prolongations of which formed a loosely knit stroma. Large sections of the tumor had undergone necrosis. Many of the blood vessels in the necrotic areas throughout the tumor were thrombosed. Some of the thrombi showed recanalization. These recanalizations differed from the convolutes of newly formed neoplastic vessels, which were thin walled and were embedded in a cufflike stroma of hemangioblastic cells, totally different from the astrocytic elements of the tumor and separated from them by a sharp line of cleavage. These were observed in many instances throughout the tumor. Hyaline degenerative changes of the walls were seen frequently in the thrombosed as well as in the patent vessels. Benzidine stains showed numerous sinusoidal channels, which made up the major branches of the vascular system of this tumor. Some of these channels measured 680 microns in diameter and possessed numerous beadlike deformities. They communicated with the slender, normal intracerebral vessels (supracapillaries and capillaries) of the adjacent normal brain tissue.

CASE 16.—*Protoplasmic astrocytoma.*

This tissue was obtained at operation from an infiltrating tumor of the left temporal lobe.

Histologic Studies.—Stained specimens revealed a moderately cellular tumor consisting essentially of protoplasmic astrocytes. There was a moderate amount of stroma. The tumor appeared to be fairly vascular in these preparations.

Benzidine stains (fig. 11) revealed a vascular pattern which was regular, the meshwork consisting of channels measuring from 30 to 80 microns in diameter, connected here and there by smaller ones measuring 16 microns in diameter.

CASE 17.—*Protoplasmic astrocytoma.*

Autopsy in this case revealed a huge infiltrating neoplasm invading both frontal lobes, the basal ganglia, and the corpus callosum. There was a history of illness

Fig. 11 (case 16).—Photomicrograph (× 45) of a protoplasmic astrocytoma. Benzidine stain.

for four years. Part of the neoplasm had been removed at the Boston City Hospital three years before the patient's death. The surgical specimen removed at that time was typical of protoplasmic astrocytoma.

Histologic Observations.—Stained specimens from the tumor observed at autopsy showed a moderately cellular neoplasm consisting predominantly of plump astrocytes, with occasional multinucleated forms and a few spongioblasts. Rare mitotic figures were seen. The tumor was well vascularized, with numerous sinusoidal channels, which did not show hyperplastic changes in the walls. Benzidine stains showed a fairly vascular tumor; on the whole, the vessels were of medium size

and uniformly distributed throughout the specimens. The size varied from 20 to 40 microns, and anastomoses were infrequent.

CASE 18.—*Fibrillary astrocytoma.*

This specimen, obtained at autopsy, consisted of a large infiltrating tumor involving the whole of the right temporal lobe. It was homogeneous and grayish and was poorly demarcated from the adjacent brain tissue.

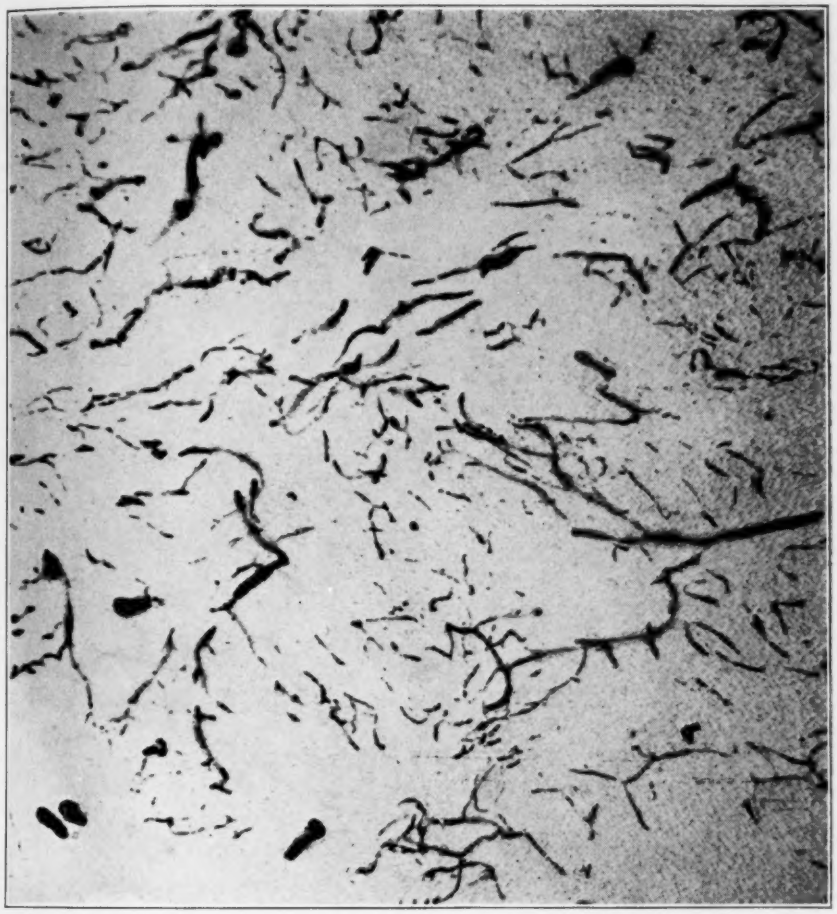

Fig. 12 (case 18).—Photomicrograph (× 83) of a fibrillary astrocytoma. Benzidine stain.

Histologic Examination.—This tumor was relatively poor in nuclei, but rich in fibrillary processes of tumor cells. Rare protoplasmic atrocytes were seen in addition to the numerous fibrillary cells. The specimen when studied with the ordinary stains appeared comparatively avascular. Benzidine stains (fig. 12) revealed an irregular network of extremely small vessels, the majority of which were precapillaries, measuring 8 to 10 microns, arranged in a wide-meshed pattern with infrequent anastomoses.

OLIGODENDROGLIOMA.—Bailey [17] stated that the rare blood vessels in this neoplasm are usually calcified. Biggart [8] noted that the blood vessels are few and not infrequently show endothelial hyperplasia.

Fig. 13 (case 20).—Photomicrograph (× 55) of an oligodendroglioma. Benzidine stain.

Bailey and Bucy,[20] in reporting a group of cases, showed that the vascularity of the tissue varies considerably, being moderate in amount

20. Bailey, P., and Bucy, P. C.: Oligodendrogliomas of the Brain, J. Path. & Bact. **32**:735, 1929.

in most of their cases. They mentioned also that in a few instances an extensive, thick network of fine capillaries is present. In oligodendrogliomas an increase in the perivascular connective tissue, proliferation of the endothelial lining of the blood vessels and calcification of the walls of vessels can be seen.

CASE 19.[21]—*Oligodendroglioma.*

At autopsy an infiltrating neoplasm involving the whole of the right temporal lobe and a portion of the occipital lobe was observed.

Histologic Observations.—Stained specimens showed a moderately cellular, uniform tumor, with a small amount of stroma. The nuclei were round, with light-staining chromatin material. Occasional mitotic figures were seen. In preparations stained with the ordinary technics the tumor appeared relatively avascular. Several areas of hemorrhage could be seen. Many calcified blood vessels were in evidence. Benzidine specimens showed that the oligodendroglioma in this case contained relatively fewer and smaller major sinusoidal channels than the tumors of the spongioastrocytic series; however, it contained a well developed capillary network, which was of greater density than that of normal gray matter. The capillary network in the oligodendroglioma was densely interlaced, but in moving the micrometer up and down at high magnification it was seen that, in spite of the dense interlacing of the network, anastomoses between the branches were comparatively rare. These capillaries extended for peculiarly long distances without dividing or anastomosing and were irregular in their course and diameter.

CASE 20.—*Oligodendroglioma.*

This specimen was removed at operation from a large invasive tumor of the right frontal lobe.

Histologic Observations.—Stained sections revealed a neoplasm composed of round nuclei with light chromatin structure and scant, pink-staining cytoplasm. Moderately frequent mitotic figures were seen. There was a fine, regular stroma. Occasional large astrocytes with hyaline-appearing cytoplasm were to be seen. The tumor appeared relatively avascular in preparations stained with the ordinary stains. Benzidine stains (fig. 13) showed, again, the same unique and characteristic vascular arrangement. There were many abnormally long, nonbranching capillaries which formed a dense mat of capillary vessels without many communications. These capillaries measured 4 microns in diameter; some extended 500 microns before branching. There were occasional large sinusoids.

MISCELLANEOUS TUMORS

PAPILLOMA OF THE CHOROID PLEXUS.—Freeman[7] reported that these neoplasms possess considerable vascularity. Davis and Cushing,[22] in a series of cases, stated that the tissues are highly vascular, with a small central core of loose connective tissue in which the blood vessels are located, the villi showing many thin-walled blood vessels.

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21. This case was previously described by Alexander and Putnam.[5]

22. Davis, L. E., and Cushing, H.: Papillomas of the Choroid Plexus, with a Report of Six Cases, Arch. Neurol. & Psychiat. **13**:681 (June) 1925.

CASE 21.—*Papilloma of the choroid plexus.*

This specimen consisted of a papillomatous tumor, the size of a golf ball, removed at operation from the ventricle of a child aged 3.

Histologic Observations.—The general pattern of the choroid plexus was preserved, with papillae in clusters of several rows about a stroma consisting of blood vessels and a loose arrangement of wide-meshed connective tissue containing fibroblasts and histiocytes. The epithelium was increased to several layers, occasional mitotic figures being seen in these cells. The benzidine stain showed rich ramification of looping vessels, most of which were 15 microns or less in diameter, the capillary ramifications being numerous. The vessels were largest in the centers of the villi and became smaller as they approached the epithelial lining.

METASTATIC CEREBRAL CARCINOMA.—Hassin and Singer [23] stated that in this condition there are dense masses of carcinoma cells grouped around distended blood vessels, which are numerous. Fried and Buckley [24] reported that the walls and lumens of blood vessels are invaded by tumor cells and that necrosis is abundant.

CASE 22.—*Metastatic carcinoma from the bronchial epithelium.*

The brain in this case showed a number of small metastatic nodules, which were part of widespread metastases in a man aged 59.

Histologic Observations.—Stained sections showed several bean-sized tumors. The neoplasm was highly cellular, the nuclei being chiefly oval, the chromatin staining moderately heavily and the cytoplasm being fairly scant. The cells were arranged in epithelial arrangement, suggesting squamous metaplasia. A great number of mitotic figures, as well as a number of small areas of necrosis, were seen. The tumor cells appeared to be fairly well demarcated from the brain. Large vascular channels and pools of blood were in evidence. Benzidine stains showed irregular channels, measuring up to 500 microns in width. Hemorrhages were common. A sharp demarcation occurred at the periphery of the tumor, the large channels merging with the vessels of the compressed white matter at this point.

CASE 23.—*Metastatic carcinoma, primary source unknown.*

This specimen was removed at operation from the right parietal region.

Histologic Observations.—The neoplasm was cellular, consisting mostly of polyhedral cells. The nuclei were vesicular, and mitotic figures were frequent. Occasional multinucleated cells, plasma cells and lymphocytes were in evidence. Areas of hemorrhage were infrequently seen. The tumor was much less vascular than that in case 22. The vascular channels in the present case averaged 60 microns in diameter, and a number of looped and twisted forms could be seen. Anastomoses in the form of capillaries were infrequent.

CASE 24.—*Metastatic carcinoma, primary source undetermined.*

Autopsy showed numerous extremely hemorrhagic metastatic nodules scattered throughout the brain.

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23. Hassin, G. B., and Singer, H. D.: Histopathology of Cerebral Carcinoma, Arch. Neurol. & Psychiat. **8**:155 (Aug.) 1922.

24. Fried, B. M., and Buckley, R. C.: Primary Carcinoma of the Lungs: IV. Intracranial Metastases, Arch. Path. **9**:483 (Feb.) 1930.

Histologic Examination.—The neoplasm was highly cellular, with poorly developed stroma. Great variability in the size and shape of nuclei was in evidence. Numerous mitotic figures and giant cells were to be seen. The cytoplasm was not abundant. This tumor was markedly hemorrhagic, containing many large lakes of blood. Benzidine stains showed a diffusely mottled picture, in which the vascular channels and hemorrhagic zones in the cellular areas predominated in a proportion of 2:1.

HEMANGIOBLASTOMA.—The characteristic wide, blood-filled channels of the hemangioblastomas are sufficiently well known to make further description superfluous. We have observed 2 instances in this series, one that of an intracranial tumor (case 25) and the other that of a tumor involving a peripheral nerve (case 26). In both the large, irregular, sinusoidal, blood-filled channels occupied a great part of each microscopic field. Not only the contents of these channels but, in addition, part of their lining was stained black with benzidine; however, this may have been an artefact due to diffusion of hemoglobin from the large masses of accumulated blood within the channels.

SUMMARY AND CONCLUSIONS

The vascular supply of tumors of the brain has been known to differ as to the number, size and density of the blood vessels. In addition, the various types of tumors of the brain, such as we have studied, are distinguished by the type of vascular pattern, sufficiently characteristic in some instances to allow a fairly accurate conjecture as to the histologic diagnosis from inspection of a benzidine preparation.

In general, two types of vascular patterns stand out. One type consists in an essentially interstitial arrangement of blood vessels, in which the vessels are mainly restricted to the zones about the edge of nodular subdivisions of the tumor while the centers of these nodules are penetrated only by comparatively few, thin branches or are completely avascular. This arrangement is found in the meningotheliomatous and psammomatous meningiomas, in the medulloblastoma and in the medulloepithelioma. The medulloblastoma is further characterized by frequent looping of sinusoid branches of comparatively uniform supracapillary size. The medulloepithelioma is characterized by a wide-meshed, roughly polygonal or spheroid network of supracapillary sinusoids and vessels, which closely hug the characteristic, densely cellular outer rims of the more cellular nodules. The centers of the more cellular nodules are avascular, while the less cellular, as it were interstitial, nodules show a regular network of smaller vessels.

The other type of pattern consists in fairly diffuse permeation of the tumor by the vascular stroma. This group includes, among others, the tumors of the spongioastrocytic series and the oligodendroglioma. The tumors of the spongioastrocytic series are characterized by a

relative paucity of true capillary channels, most of the vascular supply being made up of sinusoids of supracapillary size. In contrast to this arrangement, the oligodendroglioma exceeds all other tumors in abundance of capillaries, which, though forming a mat exceeding in density that of normal gray matter, are notable for relative infrequency of anastomoses between their densely grouped and peculiarly long, undivided channels. The vascular supply of the oligodendroglioma, which is almost exclusively capillary, may easily fail to attract attention in specimens stained by the ordinary methods, so that such specimens may give the false appearance of avascularity.

The size, density of distribution and irregularity of diameter of the sinusoids in the tumors of the spongioastrocytic series in general decrease as the degree of differentiation increases, namely, in the following order: spongioblastoma multiforme (fig. 8), spongioblastoma polare (fig. 9), astroblastoma (fig. 10), protoplasmic astrocytoma (fig. 11) and fibrillary astrocytoma (fig. 12). An exception was noted in a case of protoplasmic astrocytoma in which there was associated hemangioblastomatosis of its vascular stroma. In this instance the vascular pattern was reminiscent of that present in spongioblastoma multiforme. The polar spongioblastoma shows characteristic "shrub" and "wind-swept tree" formations (fig. 9), as well as occasional small rete mirabile formations. The "shrub" and "wind-swept tree" formations are reminiscent of the "palisades" and "braids" of the cellular arrangement.

A papilloma of the choroid plexus showed the looping characteristic of the villi of the choroid plexus. Hemangioblastomas and metastatic tumors show the characteristic large, irregular sinusoid reservoirs of blood.

The vascular supply of all the tumors of the brain studied had one feature in common, namely, an appearance suggestive of inadequacy and awkwardness of circulation, as compared to that of normal brain tissue. This may be one of the factors responsible for the frequent incidence of widespread necrosis, which occurs in certain of these neoplasms in a varying degree.

PHYSIOLOGIC SIGNIFICANCE OF THE CREATININE COEFFICIENT AND THE CREATINE TOLERANCE TEST

A CRITICAL REVIEW

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Folin [1] as a result of his classic studies on protein metabolism in 1905 came to the conclusion that the daily creatinine output of a given person is more or less constant, is influenced by the body weight and is independent of a diet which does not contain creatine or creatinine. At this time he introduced the term "creatinine coefficient," which may be defined as the amount in milligrams of creatinine or creatinine nitrogen excreted daily per kilogram of body weight. Also, since the excretion of creatinine is independent of the diet, it is considered to represent the "endogenous metabolism" of the body, as compared to the excretion of urea, which represents the "exogenous metabolism." In Shaffer's [2] view, the output of creatinine represents not necessarily the endogenous metabolism but only one special phase thereof, which takes place largely, if not wholly, in the muscles. This view was later adopted by Myers and Fine [3] and by others, who stated that muscle creatine is transformed into urinary creatinine.

The physiologic significance of the creatinine coefficient was never questioned until recently.[4] Also, in spite of much evidence to the contrary, the view that body creatine is changed into creatinine was so well established that experimental proof of this transformation was not considered necessary.

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1. Folin, O.: Approximately Complete Analyses of Thirty Normal Urines, Am. J. Physiol. **13**:45, 1905.

2. Shaffer, P. A.: The Excretion of Kreatinin and Kreatin in Health and Disease, Am. J. Physiol. **23**:1, 1908.

3. Myers, V. C., and Fine, M. S.: The Metabolism of Creatine and Creatinine: I. The Creatine Content of Muscle Under Normal Conditions; Its Relation to Urinary Creatinine, J. Biol. Chem. **14**:9, 1913.

4. Beard, H. H.: A Biometric Study of the Relation Between the Excretion of Creatinine Nitrogen and Several Body Measurements, Human Biol. **4**:351, 1932.

According to Hunter,[5] the creatinine coefficient for males varies from 18 to 32, and for females, from 9 to 26. Corpulent or even moderately corpulent subjects yield less creatinine in the urine per unit of body weight than do lean ones. Moderately corpulent persons eliminate 20 mg. of creatinine per kilogram of body weight in twenty-four hours, while lean ones yield about 25 mg. per kilogram. The day to day variations in the creatinine coefficient often exceed 10 to 25 per cent.

Garot [6] stated that in infants the creatinine excretion is not proportional to the muscular mass. Terroine and Garot [7] studied the excretion of creatine and creatinine in various warm-blooded animals with heat production of very different intensities. They found that the daily creatinine output of the rat was 60 mg. per kilogram of body weight as compared with 16 mg. per kilogram for the horse. From these observations they concluded that the excretion of creatinine in no way constitutes a measure of the muscular mass.

It is paradoxic that Folin [8] himself probably supplied the first evidence that his creatinine coefficient had little, if any, physiologic significance, although he did not offer this interpretation of his results. He showed that creatine is not transformed into creatinine in the body, a finding which has since been confirmed by numerous investigators, including ourselves. This negative evidence of a creatine-creatinine transformation has not, however, been accepted by Hunter [5] and many other students of creatine and creatinine metabolism.

There are several criticisms that one might offer of the conclusions of Folin in regard to his creatinine coefficient. He used only a few subjects and, while his results are no doubt correct for them, they would not necessarily hold if large numbers of different subjects were studied. With this idea in mind, Beard [4] made a study of the creatinine output of 400 male medical students given a normal, a high protein and a low protein diet. It was observed that there was no relation between the body weight of these students and their creatinine nitrogen output. The correlation coefficient between these two variables was found to be 0.13 ± 0.03, and the physiologic significance of the creatinine coefficient

5. Hunter, A.: Creatine and Creatinine, New York, Longmans, Green & Co., 1928.

6. Garot, L.: Contribution à l'étude des troubles du métabolisme clinique dans de la nutrition grave du nourrisson, Rev. franç. de pediat. **6**:265, 1930.

7. Terroine, E. F., and Garot, L.: L'excretion de la creatinine et la grandeur de la depense energetique des homeothermes, Arch. internat. de physiol. **27**:69, 1926.

8. Folin, O.: The Chemistry and Biochemistry of Creatine and Creatinine, in Festschrift Olaf Hammarsten, zu seinem fünfundsechzigsten Geburtstage gewidmet, Upsala, 1906.

was therefore doubted. These results were confirmed in a study of a second group, consisting of 122 students, and by published results of other authors. Chanutin and Kinard [9] observed no relation between the content of creatine in the muscle and the creatinine coefficient in several species of animals. They analyzed the data of Myers and Fine [3] for the creatine concentration of fresh muscle and the creatinine coefficient in rabbits and found the correlation coefficient between these two variables to be 0.26 ± 0.19. It may, therefore, be said that these data fail to show that muscle creatine is the parent substance of urinary creatinine. They do show a conversion of about 2 or 3 per cent creatine into creatinine in rabbits, a value, however, no larger than the experimental error of the method used for the determination of creatinine.

A review of the recent literature on this subject reveals that the body weight–creatinine relation as well as the creatine-creatinine transformation in the body has not met with universal acceptance. Further information on the subject is afforded by the results to be reported here. The bearing of these results will also be discussed in relation to the creatine tolerance test as used in the myopathies.

EXPERIMENTAL METHOD

Four groups of young white rats and 6 men served as experimental subjects. Each rat was placed in a specially constructed cage which rested on a 12 inch (30.4 cm.) funnel set in a wooden stand. The specimens of urine, free from food and feces, were collected under toluene in a 100 cc. graduate. The animals were fed the stock diet of this laboratory.[10] At the end of a two day control period each animal was given a parenteral injection of a different dose of creatine or creatinine, and the effect of this treatment on the creatine-creatinine excretion in succeeding two day periods was studied. The men ingested creatine or creatinine in water solution in doses of from 0.5 to 5 Gm. Their urine was likewise collected under toluene in two day periods and was analyzed for creatine and creatinine by the usual methods. No change was made in the customary diet of any subject.

The values for total creatinine were determined by the method of Benedict and Myers [11] and those for preformed creatinine by the method of Folin,[12] pure creatinine being used as a standard. Color matching was done with the colorimeter and the electrophotometer, with comparable checks in most cases. We have shown on several occasions that the Jaffé reaction with trinitrophenol in

9. Chanutin, A., and Kinard, F. W.: The Relationship Between Muscle Creatine and Creatinine Coefficient, J. Biol. Chem. **99**:125, 1932.

10. Beard, H. H., and Boggess, T. S.: The Effect of Parenteral Injection of Amino Acids and Related Substances upon Creatine Formation and Storage in the Rat, J. Biol. Chem. **114**:771, 1936.

11. Benedict, F. G., and Myers, V. C.: The Determination of Creatine and Creatinine, Am. J. Physiol. **18**:397, 1907.

12. Folin, O.: On the Determination of Creatinine and Creatine in Urine, J. Biol. Chem. **17**:469, 1914.

alkaline solution in muscle filtrates and urine is specific for creatinine. This specificity was shown by the use of the specific creatinine enzyme of Miller and Dubos.[13]

In one study the effect of injection of creatinine on muscle creatine was studied, the creatine content (total creatinine) of the muscle tissue being determined by the method of Rose, Helmer and Chanutin.[14] The creatinine content of the muscle tissue was determined by the trinitrophenol extraction method of Folin.[12]

RESULTS

Charts 1 and 2 show that the injection of creatinine in rats (in doses of from 10 to 200 mg.) caused an increase in the total amount of creatine excreted which was inversely proportional to the dose of creatinine injected. The percentage of conversion of the retained creatinine into creatine ranged from 480 for the 10 mg. dose of creatinine

Effect of Parenteral Injection of Creatinine on the Creatine-Creatinine Content of Muscle Tissue (Animal Experiments)

No. of Animals	Creatinine Injected, Mg.	Average Muscle Creatine, %	Average Increase in Muscle Creatine, %	Average Muscle Creatinine, %	Duration of Experiment, Days
48	Control	0.42	....	0.02	2
6	Control	0.42	....	0.02	2
2	10	0.50	19.0	0.01	2
2	20	0.49	16.6	0.01	2
2	30	0.55	30.9	0.01	2
2	40	0.51	21.4	0.01	2
2	50	0.50	19.0	0.01	2
2	60	0.48	14.3	0.02	2
2	75	0.54	28.6	0.03	2
2	100	0.56	33.3	0.03	2
2	150	0.59	40.5	0.03	2
2	200	0.53	26.2	0.03	2

to 48 for the 200 mg. dose. Chart 3 shows that the injection of creatine in doses of from 25 to 200 mg., instead of increasing the creatinine excretion, actually caused a retention of creatinine, which also varied inversely with the dose of creatine injected. When 25 mg. of creatine was injected the creatinine retention was 74 mg., or 300 per cent; 200 mg. of creatine caused a retention of 63 mg. of creatinine, or 31.5 per cent. These results show definitely that creatine is not changed into creatinine. Over half of the injected creatine and creatinine was retained in the body, and this fact may account for our unusual results.

13. Miller, B. F., and Dubos, R.: Determination by a Specific, Enzymatic Method of the Creatinine Content of the Blood and Urine from Normal and Nephritic Individuals, J. Biol. Chem. **121**:457, 1937.

14. Rose, W. C.; Helmer, O. M., and Chanutin, A.: A Modified Method for the Estimation of Total Creatinine in Small Amounts of Tissues, J. Biol. Chem. **75**:543, 1927.

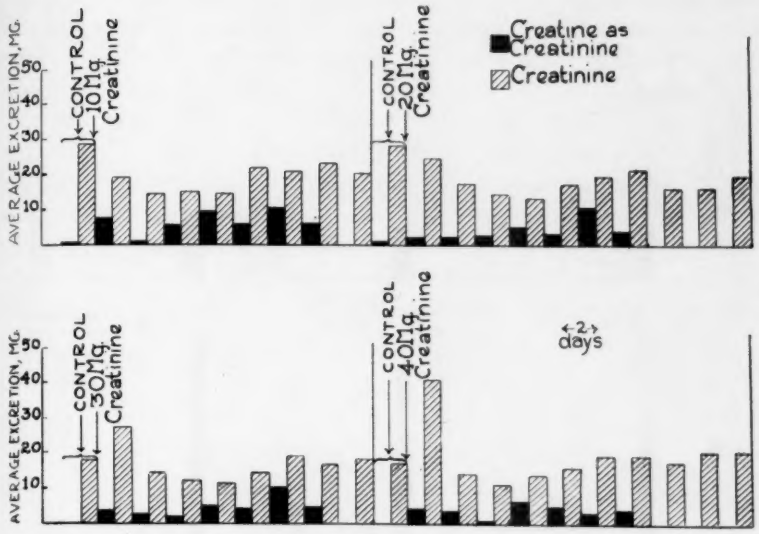

Chart 1.—Effect of parenteral injection of creatinine on creatine-creatinine excretion. Rats were used as experimental animals.

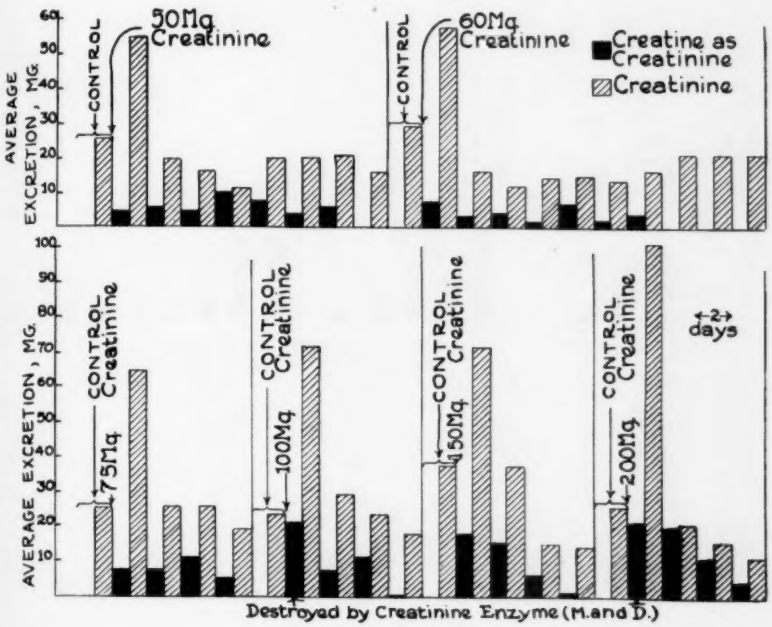

Chart 2.—Effect of parenteral injection of creatinine on creatine-creatinine excretion. Rats were used as experimental animals.

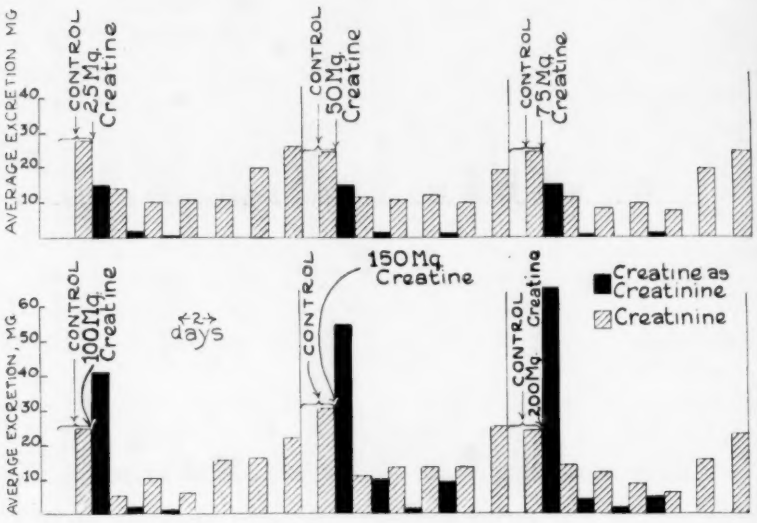

Chart 3.—Effect of parenteral injection of creatinine on creatine-creatinine excretion. Rats were used as experimental animals.

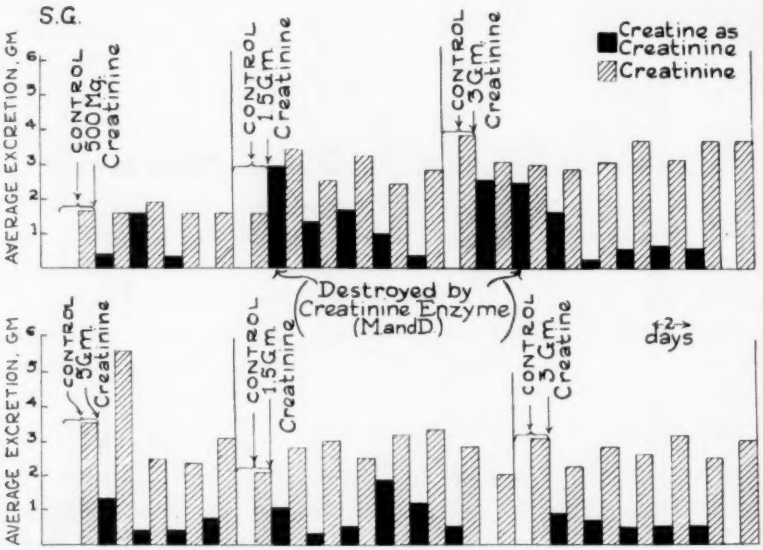

Chart 4.—Effect in subject S. G. of the ingestion of creatine and creatinine on creatine-creatinine excretion.

It was also observed that the injection of the aforementioned doses of creatinine in rats caused increases in muscle creatine varying from 14 to 41 per cent above normal (table). This fact proves that creatinine takes up a molecule of water in the muscles (a system containing about 75 per cent water) and is transformed into creatine. This observation confirms the results of Mellanby [15] and of Myers and Fine [16] in this connection. Injection of creatinine did not increase the creatinine content of the muscle tissue.

These unusual results with rats were confirmed with the 6 men used in the study. Charts 4, 5, 6 and 7 show the rate of creatine-creatinine excretion of 4 subjects when these substances were ingested in water

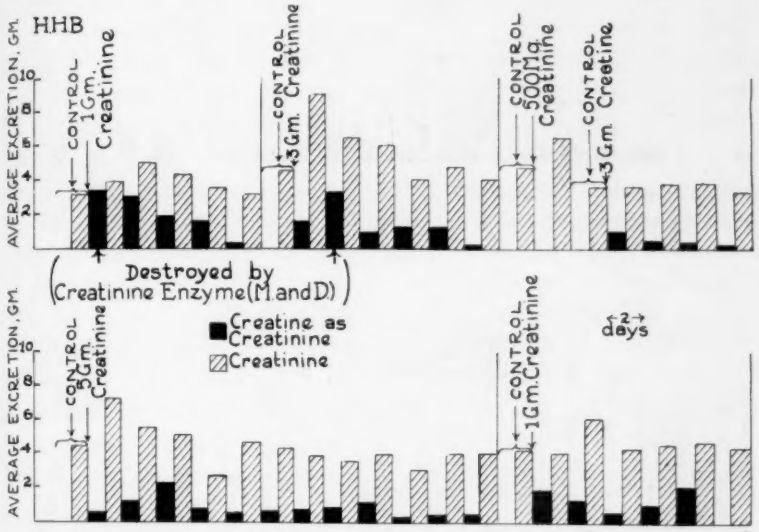

Chart 5.—Effect in subject H. H. B. of the ingestion of creatine and creatinine on creatine-creatinine excretion.

solution. It is again seen that the extra creatine excretion after ingestion of creatinine varied inversely with the dose of creatinine ingested. So large were these increases that one must conclude that creatinine stimulates enormously the excretion of both creatine and creatinine in the urine. It is also observed from these charts that the ingestion of creatine in doses of from 3 to 5 Gm. did not cause an increase in the average excretion of creatinine in man. In three of these studies we proved that the increases in the color of the Jaffé reaction with trinitrophenol in alkaline solution were due to creatinine alone.

15. Mellanby, E.: Creatin and Creatinin, J. Physiol. **36**:447, 1908.

16. Myers, V. C., and Fine, M. S.: The Influence of the Administration of Creatine and Creatinine on the Creatine Content of the Muscle, J. Biol. Chem. **16**:169, 1913.

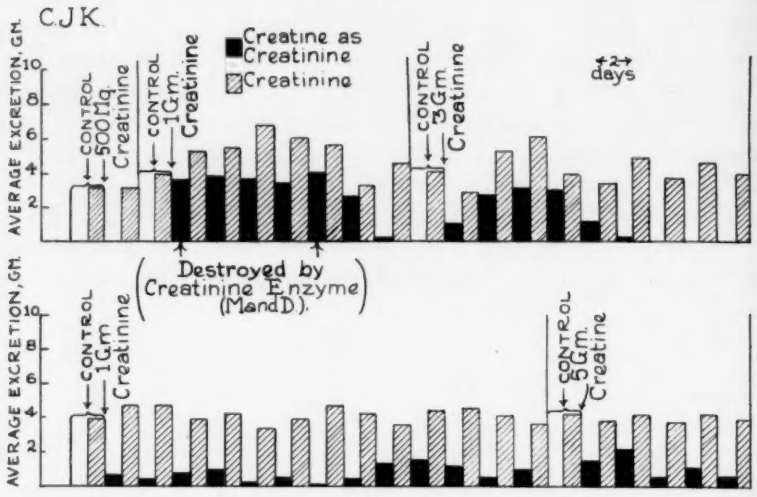

Chart 6.—Effect in subject C. J. K. of the ingestion of creatine and creatinine on creatine-creatinine excretion.

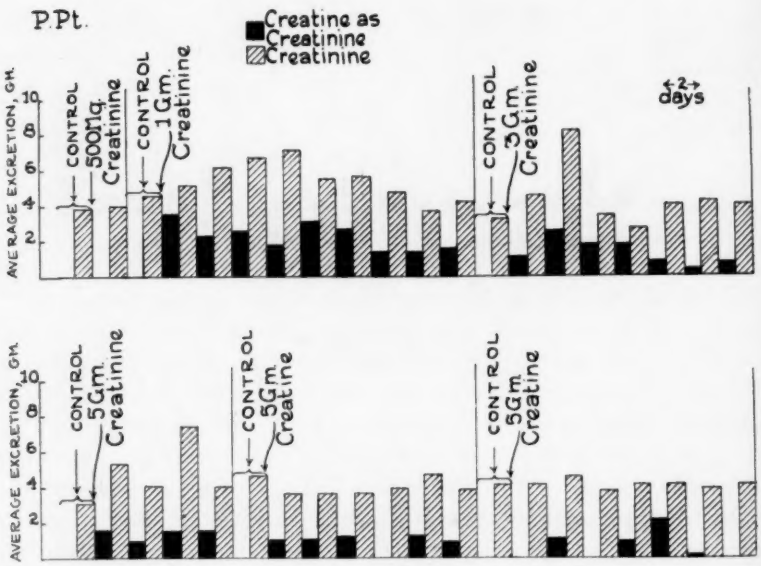

Chart 7.—Effect in a subject P. Pt. of the ingestion of creatine and creatinine on creatine-creatinine excretion.

COMMENT

Creatinine Coefficient.—We shall now discuss these results in relation to the physiologic significance of the creatinine coefficient. From these studies it is evident that creatine was not changed into creatinine. Since most of the body creatine is contained in the muscles, it is evident that body weight or, more correctly, muscle weight, does not influence the creatinine output. This confirms the earlier findings of one of us [4] as well as those of Chanutin and Kinard.[9] In fact, the reverse reaction occurs, in which creatinine is changed into muscle creatine, the excess of the latter then being excreted into the urine. In other studies [17] it has been shown that the liver must be present to prevent creatinuria but that it does not play any part in creatine formation or in creatinine excretion in the urine.

It is our belief that both creatine and creatinine arise from the amino acids in normal metabolism. Creatinine may be formed in amounts larger than is generally believed. For instance, if 2 Gm. of creatinine were formed daily, about 1.5 Gm. would be excreted; the remainder would undergo other transformations, one of which would be a transformation into creatine. Since creatinuria does not occur in men with normal hepatic function, any extra creatine formed would not be transformed into creatinine but possibly into such other products as glycocyamine, dimethylamine or methylguanidine, since these substances have been found in the urine under different conditions of metabolism.[18]

Benedict and Behre [19] denied the existence of creatinine in the blood. Miller and Dubos,[13] however, using their specific creatinine enzyme, have shown that most of the Jaffé reactive material of the plasma is actually creatinine. This is the view expressed by many recent workers. Since the presence of creatinine in the blood has been established, creatinine is evidently, according to Goudsmit,[20] the parent substance of the creatinine of the urine.

17. Beard, H. H.: The Relation of the Liver to Creatine-Creatinine Metabolism, Am. J. Physiol. **124**:530 (Nov.) 1938.

18. Bodansky, M.: Comparison of Glycine and Guanidine Acetic Acid as Precursors of Creatine, J. Biol. Chem. **115**:641, 1936. Weber, C. J.: Isolation of Glycocyamine from Urine, Proc. Soc. Exper. Biol. & Med. **32**:172, 1934. Kapeller-Adler, R., and Toda, K.: Ueber das Vorkommen von Monomethylamin im Harn, Biochem. Ztschr. **248**:403, 1932. Sullivan, M. X.; Hess, W. C., and Irrevere, F.: Studies on Muscular Dystrophies: The Presence of Simple Guanidine Derivatives in the Urine, J. Biol. Chem. **114**:647, 1936.

19. Benedict, S. R., and Behre, J. A.: Studies in Creatine and Creatinine Excretion: IV. On the Question of the Occurrence of Creatinine and Creatine in Blood, J. Biol. Chem. **52**:11, 1922.

20. Goudsmit, A.: The Origin of Urinary Creatinine, J. Biol. Chem. **115**: 613, 1936.

That there is no biologic relation between creatine and creatinine has been recently shown by the following investigators: Terroine and Boy;[21] Zickelbein;[22] Thomas, Milhorat and Techner;[23] Daniels and Hejinian,[24] and Catherwood and Stearns.[25] What they meant is that creatine is not changed into creatinine, a view we accept. On the other hand, we have shown in this study that there is an important biologic relation between creatinine and creatine.

Most of the studies showing that muscle creatine is probably the mother substance of urinary creatinine were made before the function and distribution of creatine in the muscles were known. About four fifths of the muscle creatine is present as phosphocreatine, the remainder being free.[26] We have observed that the muscles of rats can take up over 100 per cent of extra creatine for a short period [27] and that the administration of small amounts of this substance does not produce an excess of creatinine. Evidently the muscles can absorb these small amounts of creatine without any change in the creatinine excretion. It is well known that during muscular contraction phosphocreatine is being continually hydrolyzed and synthesized, and there is no evidence that it can be transformed into urinary creatinine.

Folin [1] observed that the excretion of creatinine is an index of the endogenous metabolism, a view which has been generally accepted. This type of metabolism, however, does not occur when a person eats three meals a day. Since creatinine can be changed into creatine and since it stimulates the excretion of both creatine and creatinine, it is evident that creatine is produced in the body in amounts larger than can be accounted for on any basis of endogenous metabolism.

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21. Terroine, E. F., and Boy, G.: La répartition des representants urinaires du métabolisme azoté et sa signification physiologique: V. Le métabolisme proteique exogène, Bull. Soc. chim. biol. **15**:1163, 1933.

22. Zickelbein, U.: Ueber die Kreatin-Kreatininausscheidung mit dem Harn bei fleischfreier und fleischhaltiger Nahrung, Ztschr. f. d. ges. exper. Med. **87**: 112, 1933.

23. Thomas, K.; Milhorat, A. T., and Techner, F.: Weitere Untersuchungen über die Herkunft des Kreatins, Ztschr. f. physiol Chem. **214**:121, 1933.

24. Daniels, A. L., and Hejinian, L. M.: Growth of Infants from the Standpoint of Physical Measurements and Nitrogen Metabolism: Creatine, Am. J. Dis. Child. **38**:499 (Sept.) 1929.

25. Catherwood, R., and Stearns, G.: Creatine and Creatinine Excretion in Infancy, J. Biol. Chem. **119**:201, 1937.

26. Eggleton, P.: The Diffusion of Creatine and Urea Through Muscle, J. Physiol. **70**:294, 1930.

27. (*a*) Beard, H. H., and Pizzolato, P.: Further Observation on the Effect of Amino Acids and Related Substances upon Creatine Formation and Storage in the Rat: A New Theory of the Origin of Creatine in the Animal Body, J. Biochem. **28**:421, 1939. (*b*) Beard and Boggess.[10]

The fact that creatine excretion is inversely proportional to creatinine injection has been observed in other studies in this laboratory.[28] It is logical to believe that creatinine may be a mother substance of the creatine that is excreted in the urine of patients suffering from the various myopathies. Tripoli and Beard [29] studied 51 patients with myopathies of various types over a three year period. An average daily excretion of 0.9 Gm. of creatinine and 0.6 Gm. of creatine was observed. The normal daily output of creatinine is about 1.5 Gm. Thus the average creatinine retention ($1.5 - 0.9 = 0.6 \times 1.16 = 0.69$ Gm. of creatine) is quantitatively accounted for by the extra creatine excretion. Somewhat the same results were obtained by Milhorat and Wolff [30] in their patients, who exhibited a progressive decrease in creatinine excretion, which was accompanied by a progressive increase in creatine excretion.

In the past it has usually been considered that this creatine takes origin from the disintegrating muscle fibers in the myopathies, though this is probably not the case. It is well known that these fibers are not able to utilize the creatine brought to them, which results in its excretion in the urine. Milhorat and Wolff [30] suggested that the defect in creatine-creatinine metabolism might be taken as an index of the amount of improperly functioning muscle tissue rather than of the amount of wasted muscle. These muscle fibers may be affected chemically long before visible signs of wasting are seen.

It is generally believed that protein feeding does not lead to increases in creatinine output. But if sufficient amounts of the amino acids, such as 5 or 10 Gm. at one time, are ingested, as is usually advised in aminoacetic acid therapy for myopathy, both the creatine and the creatinine excretion may be increased. Recently Beard and Boggess [31] showed that in the majority of their experimental animals the injection of aminoacetic acid, alanine and arginine caused an increase in creatinine

28. (*a*) Beard, H. H., and Pizzolato, P.: The Effect of Parenteral Injection of Purines, Methylated Purines, and Various Drugs upon Creatine-Creatinine Metabolism, J. Pharmacol. & Exper. Therap. **63**:306, 1938. (*b*) Pizzolato, P., and Beard, H. H.: The Relation of the Hormones to Creatine-Creatinine Metabolism: I. Anterior Pituitary Hormones, Theelin and Testosterone Propionate, Endocrinology **24**:358, 1939. (*c*) Jacob, E. J., and Beard, H. H.: The Biological Relation of Creatine and Creatinine, to be published.

29. Tripoli, C. J., and Beard, H. H.: Review of Metabolic and Clinical Studies in Amino Acid Therapy, South. M. J. **31**:662, 1938.

30. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937.

31. Beard, H. H., and Boggess, T. S.: The Effect of Parenteral Injection of Amino Acids upon Creatine-Creatinine Excretion, J. Biochem. **27**:231, 1937.

excretion. Mourot [32] showed that all the amino acids, and especially arginine, histidine and aminoacetic acid, also increase creatine excretion. Beard and Pizzolato [27a] showed that the injection of all the amino acids of the protein molecule except proline and oxyproline causes large increases in muscle creatine. Boy [33] observed that creatine arises during fasting not from the minimal nitrogen metabolism but from the excess protein catabolism. Creatine, she claimed, is formed from exogenous proteins. These results confirm those of Beard and his co-workers in this connection [34] and demonstrate that the amino acids are the most logical precursors of both creatine and creatinine. If this is true, it would seem that weight plays only a secondary role in creatinine excretion and that the rate of protein catabolism plays the primary role in this connection.[4]

Creatine Tolerance.—Since the introduction of amino acid therapy for the myopathies the creatine tolerance test has become a routine clinical procedure. This test, according to Thomas,[35] depends on three factors of unknown magnitude, since alimentary creatinuria occurs when the capacity of the tissues and blood for degradation and storage no longer suffices and when the renal threshold is exceeded. That the liver also plays an important part in preventing creatinuria has been shown by Beard.[17] Creatinuria is known to occur in many conditions other than the myopathies, such as diabetes, diseases of the liver, endocrine imbalance, starvation and carbohydrate deprivation. Before the creatine tolerance test can have any physiologic significance these conditions must be ruled out. It is likely that carbohydrate metabolism is affected in the patient with myopathy and little is known of the physiologic status of the liver of such a patient. It has also been observed by Haldi and his co-workers [36] that ingestion of dextrose and fructose by man results in creatinuria.

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32. Mourot, G.: Les produits excrémentitiels du catabolisme azoté et leur origine; les termes ultimes de la dégradation des divers acides aminés, Bull. Soc. chim. biol. **19**:1209, 1937.

33. Boy, G.: La répartition des représentants urinaires du métabolisme azoté et sa signification physiologique; l'inanition, Bull. Soc. chim biol. **16**:1009, 1934.

34. Beard, H. H., and Barnes, B. O.: The Influence of Feeding Proteins, Amino Acids and Related Substances upon Creatine-Creatinine Metabolism, J. Biol. Chem. **94**:49, 1931. Footnote 27.

35. Thomas, K.: The Metabolism of Creatine and Creatinine, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1938, vol. 7, p. 211.

36. Bachmann, G.; Haldi, J.; Ensor, C., and Wynn, W.: The Effects of the Ingestion of Glucose and Fructose on the Rate of Excretion of Urine and Various Constituents, Am. J. Physiol. **124**:77, 1938.

It has been shown by Milhorat and Wolff [30] and by Cuthbertson and Maclachlan [37] that ingestion of aminoacetic acid often decreases the creatine tolerance. As suggested by the former investigators, this seems unreasonable, since this amino acid improves muscular function in some patients with myopathy who may show an impaired creatine tolerance. According to Thomas,[35] the creatine tolerance of children has no diagnostic value. The amount of creatine excreted during the creatine tolerance test depends on the size of the dose administered. This is only about 1 or 2 per cent of the amount of creatine stored in the tissues, while in the sugar tolerance test large amounts of dextrose are ingested. The chief criticism of the test is that wide variations in creatine retention and excretion are likely to occur in both normal and myopathic persons after ingestion of creatine (and of creatinine).[38] We have shown that creatine is not transformed into creatinine in the rat or in man. On the other hand, creatinine is changed into creatine in the muscles, and greatly stimulates the excretion of both creatine and creatinine in the urine when it is injected into young rats or ingested by man. While several groups of workers have concluded that there is no biologic relation between creatine and creatinine, it is certain that there is an important biologic relation between creatinine and creatine.

Further proof that creatinine takes up a molecule of water and forms creatine has recently been observed in this laboratory. The injection of 16 cc. of 0.9 per cent sodium chloride alone in young rats caused increases of from 90 to 140 mg. in creatine excretion and no increase in muscle creatine. This shows that the injected water does not "wash out" the muscle creatine into the urine. There is evidently an important relation between water metabolism and creatine synthesis in the body.

It has been shown by Milhorat and Wolff [39] and by Cuthbertson and Maclachlan [37] that the creatine tolerance in different types of myopathy may be either impaired or within normal limits. Milhorat, Techner and Thomas [40] observed that aminoacetic acid increased creatine formation

37. Cuthbertson, D. P., and Maclachlan, T. K.: The Treatment of Muscular Dystrophy with Glycine, Quart. J. Med. **27**:411, 1934.

38. (*a*) Beard, H. H.; Tripoli, C. J., and Andes, J. E.: The Diagnostic and Prognostic Significance of the Creatin-Creatinin Metabolism in Various Myopathies Before and After Amino-Acid Therapy, Am. J. M. Sc. **188**:706, 1934. (*b*) Jacob and Beard.[28c] (*c*) Tripoli and Beard.[29]

39. Milhorat, A. T., and Wolff, H. G.: (*a*) Studies in Diseases of Muscle: IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, Arch. Neurol. & Psychiat. **40**:663 (Oct.) 1938; (*b*) V. Metabolism of Creatine and Creatinine in Myotonia Congenita, Myotonia Atrophica, Amyotonia Congenita, Dystonia Musculorum Deformans and Paralysis Agitans, ibid. **40**:680 (Oct.) 1938; (*c*) footnote 30.

40. Milhorat, A. T.; Techner, F., and Thomas, K.: Significance of Creatine in Progressive Muscular Dystrophy and Treatment of This Disease with Glycine, Proc. Soc. Exper. Biol. & Med. **28**:609, 1932.

and improved creatine tolerance in some of their myopathic patients. Some clinical improvement was also observed. The improvement in creatine tolerance, however, may not have been the cause of the clinical improvement. It must not be forgotten that ingestion of aminoacetic acid serves useful functions in the body besides creatine formation, such as synthesis of proteins, transformation into dextrose, detoxication, stimulation of the appetite and increase in body weight, and that the subjective improvement observed in many patients after ingestion of aminoacetic acid may be due to increase in appetite and synthesis of protein and dextrose rather than to any effect on creatine synthesis. In cases of pseudohypertrophic and progressive muscular dystrophy in which improvement occurs, it is possible that increased protein formation may replace fat or fibroareolar tissue in the muscles of the legs. This would account for the improvement.

Milhorat and Wolff concluded that the creatine tolerance indicates the extent of muscular involvement in progressive muscular dystrophy. However, they made this statement in this connection: [39a]

> Neither the creatine output nor the creatine tolerance associated with muscular wasting subsequent to disease of the nervous system appears to be a valuable index of the amount of muscular involvement. The results of this investigation show that considerable wasting and functional impairment of important muscle groups can occur with little effect on the metabolism of creatine.

It is well known that the defect in the myopathic patient is a defect not of creatine or aminoacetic acid synthesis but of the utilization of creatine produced in the body from its precursors. It is evident, therefore, that exogenous creatine serves no useful purpose for this type of patient. On the other hand, many patients with myopathy (especially in patients in whom the disease is in an early stage or those not showing lesions in the central nervous system, myasthenia gravis and simple chronic nervous exhaustion, fatigue and underweight) are benefited by aminoacetic acid therapy. Stimulation of the appetite and increased formation of metabolic creatine from its precursors is certainly involved in the process. The latter type of creatine is then utilized by the patient. Little is known of the function of "free" creatine in the muscles. On the other hand, "bound" creatine, as phosphocreatine, is useful in supplying energy for muscular contractions.

Reinhold and Kingsley [41] studied the chemical composition of diseased muscle. Higher concentration of muscle extractives was found in some myopathies after aminoacetic acid therapy, with resulting

41. Reinhold, J. G., and Kingsley, G. R.: The Chemical Composition of Voluntary Muscle in Muscle Disease: A Comparison of Progressive Muscular Dystrophy with Other Diseases Together with a Study of Effects of Glycine and Creatine Therapy, J. Clin. Investigation **17**:377, 1937.

regeneration of the muscles. Creatine therapy, on the other hand, caused no clinical improvement and no change in the concentration of the constituents of the muscle tissue. This is further evidence that exogenous creatine does not enter into the muscle metabolism of the myopathic patient and shows that the ability of the patient to retain creatine has no physiologic significance. It was also shown by Reinhold and Kingsley, as well as by Nevin,[42] that the only distinct abnormality in myasthenia gravis is a high concentration of soluble ester phosphorus and that the creatine concentration is practically normal.

We believe with Milhorat that the diminished creatinine excretion and the extent of creatinuria are related to the degree of muscular disability, i. e., to the total mass of improperly functioning muscle, and are not an index of the amount of wasted muscle. In this connection a study was made by Beard, Tripoli and Andes [38a] of creatine excretion before and after amino acid therapy in 51 cases of myopathy.[29] Initial clinical improvement, both objective and subjective, occurred in 10 patients, and subjective improvement in 7 patients, in all of whom creatine excretion rose from 50 to 200 per cent above the control level after aminoacetic acid was given. This increased creatinuria usually disappeared within two or three weeks. On the other hand, no clinical improvement took place in 13 patients, 9 of whom were suffering from neuromuscular conditions, when the increase in creatinuria was absent or was less than 50 per cent above that of the control level before administration of aminoacetic acid. It was concluded that a study of the creatinuria before and after ingestion of aminoacetic acid offered valuable diagnostic and prognostic information in cases of myopathy.

SUMMARY AND CONCLUSIONS

Results of investigative work from this laboratory during the past thirteen years, together with a study of the creatine-creatinine relation in the rat and in man, are discussed in relation to the physiologic significance of the creatinine coefficient and creatine tolerance in the myopathies. It is believed that the evidence justifies the conclusion that the creatinine coefficient possesses little if any physiologic significance (1) because muscle creatine is not transformed into urinary creatinine; (2) because there is no relation between creatinine output and body weight, and (3) because the creatinine output depends on the rate of protein catabolism in the body.

The physiologic significance of creatine tolerance in the myopathies is also questioned (1) because certain muscles of the myopathic patient

42. Nevin, S.: A Study of Muscle Chemistry in Myasthenia Gravis, Pseudohypertrophic Muscular Dystrophy and Myotonia, Brain **57**:239, 1934.

are unable to utilize exogenous creatine brought to them; (2) because ingestion of aminoacetic acid causes an increase in metabolic creatine in the muscles with definite clinical improvement in some cases, while at the same time causing a decrease in the creatine tolerance; (3) because wide variations in creatine retention and excretion occur after its ingestion in both normal and myopathic persons, and (4) because there is a close relation between creatine synthesis and water metabolism which is not revealed by the creatine tolerance test.

A better diagnostic and prognostic test in cases of myopathy is furnished by a study of the excretion of creatine and creatinine before and after ingestion of aminoacetic acid. The disappearance of the creatinuria, with resulting clinical improvement of certain types of disease, shows the ability of the patient to utilize, rather than simply to store or tolerate, the creatine synthesized during the period of therapy.

THE HYPOTHALAMIC NUCLEI IN HEAT STROKE

WITH NOTES ON THE CENTRAL REPRESENTATION OF TEMPERATURE REGULATION

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Heat stroke is presumably a condition associated with a breakdown of the mechanisms for control of the body temperature, with resulting loss of power to adjust to an extremely high environmental temperature. In a previous investigation (Morgan [1]) it was shown that experimental fever produced in the dog and rabbit by injections of typhoid toxin is accompanied by marked chromatolysis in the nucleus tuberomamillaris and by chromatolysis of a lesser and more variable degree in the basal optic ganglia and paraventricular nucleus. Investigations bearing on the role of the hypothalamus in the regulation of body temperature have been reviewed by Fulton [2] and in the preceding paper.

A study of the diencephalon in patients suffering from heat stroke suggests the following questions: (1) Has the hypothalamus been affected by previous disease or injury, or were the vegetative centers in this region apparently normal prior to the onset of the heat stroke? (2) What acute cell changes, if any, in the hypothalamus may be associated with the characteristic fever of heat stroke? (3) Will a study of the hypothalamic centers in a condition of this sort furnish any evidence as to the nature of the temperature-regulating mechanism of the hypothalamus?

The nuclei of the hypothalamus in 13 patients who died of heat stroke were studied and compared with the nuclei of the hypothalamus in 5 control brains from patients who died of a variety of causes (malignant hypertension, gunshot wound in the back, skull fracture, pulmonary tuberculosis and mercury bichloride poisoning). The amount of cell loss, if any, in the nuclei of the hypothalamus in heat stroke was determined by counting the number of cells in two or more microscopic fields within

From the Department of Anatomy, the University of Cincinnati College of Medicine.

1. Morgan, L. O.: Cell Changes in Some of the Hypothalamic Nuclei in Experimental Fever, J. Neurophysiol. **1**:281, 1938.

2. Fulton, J. F.: Physiology of the Nervous System, London, Oxford University Press, 1938, p. 246.

each cell group and comparing this with the average number of cells in corresponding areas of the 5 control brains. An attempt was also made to determine, as far as possible, cell changes, such as chromatolysis and neuronophagia. For a more detailed description of the histologic characteristics of the hypothalamus, the sectioning and staining technic, the types of pathologic changes commonly observed in this region and the methods of evaluating these changes the reader is referred to previous papers.[3]

ABSTRACT OF CLINICAL CASES

Case 1.—Heat stroke. Woman aged 65. Maximum temperature 109 F. Generalized vascular sclerosis.

Case 2.—Heat stroke. Man aged 55. Maximum temperature 111 F. Terminal convulsions. Early generalized vascular sclerosis.

Case 3.—Heat stroke. Man aged 73. Maximum temperature 106 F. Terminal lobular pneumonia. Generalized vascular sclerosis. Atrophy of the cerebral cortex. Multiple anomalous commissures of the third ventricle.

Case 4.—Heat stroke. Man aged 53. Maximum temperature 105.8 F. Diabetes mellitus of five years' duration. Terminal convulsions. Terminal lobular pneumonia. Early generalized vascular sclerosis.

Case 5.—Heat stroke. Man aged 68. Maximum temperature 109 F. Terminal convulsions. Generalized vascular sclerosis.

Case 6.—Heat stroke. Woman aged 53. Maximum temperature 105.7 F. Chronic alcoholism. Obesity. Visceral evidences of severe toxemia.

Case 7.—Heat stroke. Man aged 78. Maximum temperature 104.5 F. Generalized vascular sclerosis. Atrophy of the cerebral cortex. Nonsyphilitic ulcerative colitis. Miliary erosions of the gastric mucosa.

Case 8.—Heat stroke. Man aged 63. Maximum temperature 109 F. Probable acute alcoholism. Hemorrhage into the mesocolon and the body and tail of the pancreas. Syphilitic aortitis.

Case 9.—Heat stroke. Man aged 79. Maximum temperature 103.8 F. Generalized vascular sclerosis. Adenocarcinoma of the stomach. Atrophy of the cerebral cortex; old area of softening in the right internal capsule.

Case 10.—Heat stroke. Man aged 52. Maximum temperature 108 F. Syphilitic heart disease; aortic insufficiency; early vascular sclerosis. Old area of softening in the right putamen.

Case 11.—Heat stroke. Man aged 40. Maximum temperature 108.2 F. Autopsy limited to the head.

Case 12.—Heat stroke. Man aged 63. Maximum temperature 109.4. F. Generalized vascular sclerosis.

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3. Morgan, L. O.: The Nuclei of the Region of the Tuber Cinereum, Arch. Neurol. & Psychiat. **24**:267 (Aug.) 1930. Morgan, L. O., and Gregory, H. S.: Pathological Changes in the Region of the Tuber Cinereum in Idiopathic Epilepsy, Am. J. Psychiat. **9**:805, 1930. Morgan, L. O.; Vonderahe, A. R., and Malone, E. F.: Pathological Changes in the Hypothalamus in Diabetes Mellitus, J. Nerv. & Ment. Dis. **85**:125, 1937.

CASE 13.—Heat stroke. Man aged 70. Maximum temperature 107.6 F. Generalized vascular sclerosis. Lobular pneumonia, thrombophlebitis of the right femoral vein; massive pulmonary infarction of the right lung.

Eleven of the 13 patients with heat stroke were men. Twelve of the 13 were 50 years of age or older.

In all 12 cases in which complete autopsy was performed heat stroke was associated with some pathologic process tending to produce degenerative changes in the central nervous system: In 9 it was associated with generalized vascular sclerosis; in 2, with syphilis and in 1, with chronic alcoholism.

OBSERVATIONS AND COMMENT ON PATHOLOGIC CHANGES

Although 5 control brains were used as a direct standard of comparison with those in the 13 cases of heat stroke, over 100 additional

Summary of the Pathologic Alterations in the Hypothalamus in Heat Stroke

	Paraventricular Nucleus		Basal Optic Ganglia		Nucleus Tuberis Lateralis		Nucleus Tuberomamillaris		Substantia Grisea	
Case No.	Cell Loss, %	Normal Cells, %	Cell Loss, %	Normal Cells, %	Cell Loss, %	Normal Cells, %	Cell Loss, %	Normal Cells, %	Cell Loss, %	Normal Cells, %
1	30	72	None	50	56	23	?	8	24	50
2	16	85	None	92	39	86	None	18	None	68
3	41	64	None	88	49	18	None	22	None	88
4	30	50	16	78	42	78	None	24	None	72
5	25	85	20	88	31	76	None	27	None	80
6	17	72	None	76	46	30	None	28	None	76
7	29	82	None	84	34	62	None	30	None	80
8	26	83	None	82	44	66	None	30	None	82
9	30	66	None	80	35	27	?	32	None	62
10	25	65	None	78	33	16	None	32	None	50
11	28	85	None	96	40	82	None	33	None	72
12	28	82	13	78	32	30	None	33	None	72
13	25	86	25	62	36	22	None	36	None	90

brains in which a study had been made of the nuclei of the diencephalon were also utilized. These represented 30 cases of epilepsy, 32 cases of psychoses, 15 cases of diabetes mellitus and 25 miscellaneous cases in which death was ascribed to a variety of causes. These brains also served as useful controls in so far as they formed a background for interpretation of the results of the present study, by indicating the manner in which the nuclei of this region react to a variety of conditions other than heat stroke.

In heat stroke one is apparently dealing with two types of pathologic change (table). The first type, observed in the nucleus paraventricularis, the nucleus tuberis lateralis and occasionally the basal optic ganglia (nucleus supraopticus), suggests a condition in which there has been considerable damage in the past, with cell degeneration in most instances taking place at a slow rate at the time of death. The second type, well illustrated in the nucleus tuberomamillaris, to a

less degree in the substantia grisea and sometimes in the basal optic ganglia, suggests acute cell changes, without an appreciable amount of cell loss. This point will be dealt with more fully in the following description.

Nucleus Paraventricularis.—There was marked cell loss in this nucleus in each of the 13 cases of heat stroke. This cell loss ranged from 16 per cent, in case 2, to 41 per cent, in case 3. The average amount of cell loss in this group was 27 per cent. The number of normal cells in this nucleus ranged from 50 per cent, in case 4 (heat stroke and diabetes), to 88 per cent, in case 14. The average number

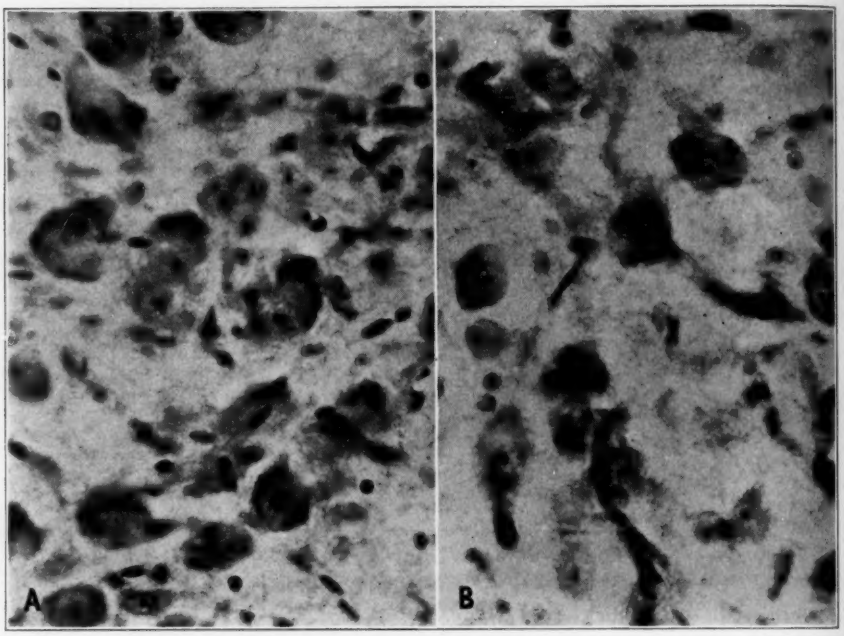

Fig. 1.—Photographs of the paraventricular nucleus illustrating the cell loss in cases of heat stroke. *A* indicates the nucleus in a brain used as a control; *B*, the nucleus in the brain of a patient who died of heat stroke (case 11).

of normal cells comprised 75 per cent of the total. In the 5 control brains the number of normal cells ranged from 89 to 98 per cent, with an average of 93 per cent. In 8 of 13 cases of heat stroke, 82 per cent or more of the cells were normal.

In the 120 human brains studied to date, pathologic changes were noted constantly in the paraventricular nucleus only in association with diabetes mellitus (15 cases) and heat stroke (13 cases). With the exclusion of case 4, in which the condition was complicated by diabetes, we observed in the cases of heat stroke an average cell loss of

27 per cent, as compared with an average of 40 per cent in those of diabetes. In cases of heat stroke we observed an average of 77 per cent of normal cells, as compared with an average of only 36 per cent in those of diabetes. This comparison suggests the possibility that in diabetes one is dealing with pathologic changes which continue rather rapidly up to the time of death. In heat stroke, on the other hand, one is dealing with pathologic changes which have progressed slowly over a longer period, or with degenerative changes which were more acute at some time in the patient's history and then almost, if not entirely, subsided before the time of death. The fact that the chromatolysis observed in this nucleus was almost entirely in the earlier stages and that cells in the final process of dissolution were almost never seen might be taken to indicate that the cell loss in this nucleus represents past history while the chromatolysis is incidental to the heat stroke.

The nucleus paraventricularis is composed of cells which differ greatly in size. There are many large cells, which are comparable with the cells of the basal optic ganglia. There are, in addition, many cells which are less than one-half the size of the larger cells. Finally, there are cells which are intermediate in size between the small and the large cells. In this transition from small to large cells it is difficult to draw a sharp line of distinction and to set up a definite classification on the basis of size. It is apparent, however, that in heat stroke there is almost complete destruction of the large cells, and hence the surviving cells are almost entirely of the small and intermediate types. In diabetes, on the other hand, the cell loss is almost entirely confined to the small and medium-sized cells, while the large cells survive.

Nucleus Tuberis Lateralis.—This nucleus was markedly affected in every case of heat stroke (fig. 2). The amount of cell loss ranged from 31 per cent, in case 5, to 56 per cent, in case 1. The average cell loss for the group was 40 per cent. The relative number of normal cells in this group showed a wide range of variation, from 16 per cent, in case 10, to 86 per cent, in case 3. The average for the group was 47 per cent of normal cells. In the 5 control brains the number of normal cells was 60, 50, 80, 66 and 70 per cent, respectively, or an average of 65 per cent. Here, again, the appearance of this cell group suggests that the cell destruction had occurred some time prior to the onset of heat stroke.

In the 120 brains which have been studied to date the nucleus tuberis lateralis was more frequently involved than any other cell group. In every case of epilepsy (56 per cent) and of heat stroke a striking amount of cell loss was exhibited. Cell loss (28 per cent) was apparent in 28 of the 32 cases of psychoses. Of the 15 cases of diabetes there was cell loss (25 per cent) in 7 (in 5 of which there were psychic

abnormalities). Also, in the miscellaneous group of cases cell loss in this nucleus was not infrequent. In the brains which showed cell loss the proportion of normal cells was 14 per cent in cases of epilepsy, 26 per cent in cases of psychoses and 48 per cent in cases of diabetes, as compared with 47 per cent of normal cells in cases of heat stroke. The significance of the frequency with which this nucleus is affected in a large variety of conditions presents a problem which merits further investigation.

Nucleus Tuberomamillaris (Mamilloinfundibularis).—This cell group exhibited similar alterations in all the 13 cases of heat stroke (table).

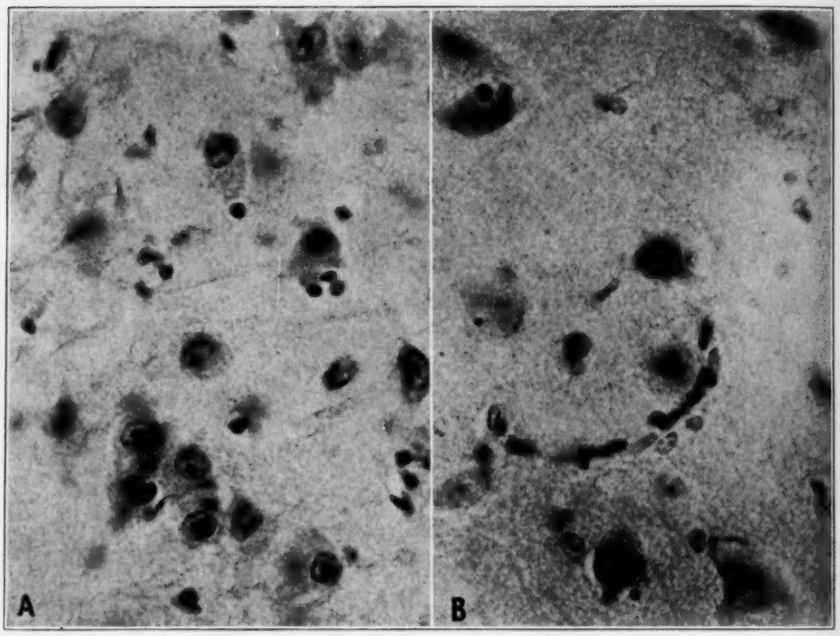

Fig. 2.—Photographs of the nucleus tuberis lateralis illustrating the cell loss in cases of heat stroke. *A* indicates the nucleus in a brain used as a control; *B*, the nucleus in the brain of a patient who died of heat stroke (case 11).

The fact that the cells of this group are scattered through the tuber rather than collected into a well circumscribed nucleus makes it impossible to secure accurate cell counts in a given area. With the possible exception of cases 1 and 9, however, the cells of this nucleus appeared normal in number and distribution. In these 2 questionable cases there was little or no cell loss. There was a considerable amount of chromatolysis in all the cases of heat stroke (fig. 3). The number of normal cells remaining in the nucleus tuberomamillaris ranged from 8 per cent, in case 1, to 36 per cent, in case 13. For the entire group

of cases there was an average of 27 per cent of normal cells. In the control brains, 95 per cent or more of the cells were normal in appearance. All grades of chromatolysis were represented, except that we rarely saw any cells in the final process of dissolution. There was a remarkable resemblance between the cell picture presented in heat stroke

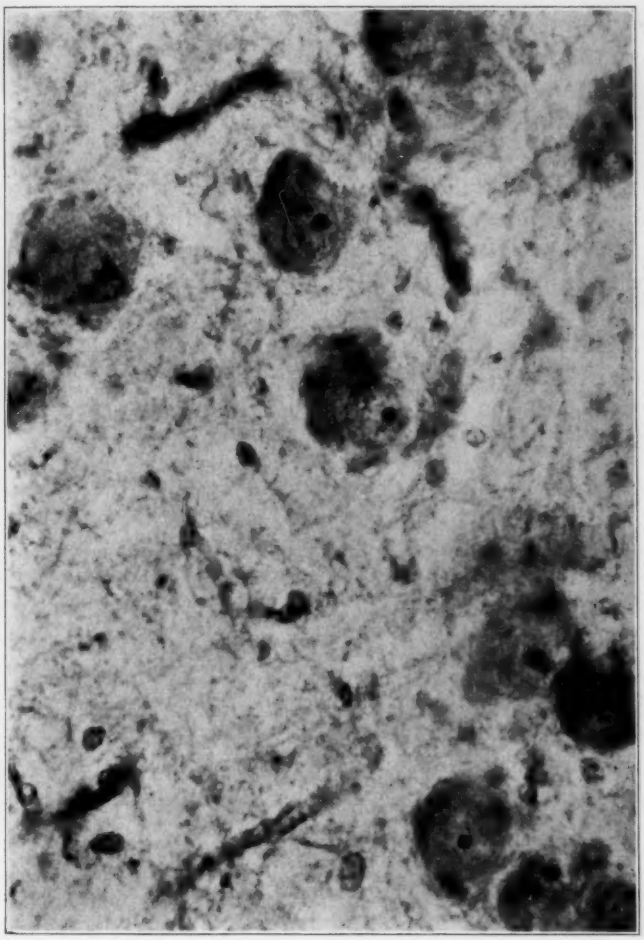

Fig. 3.—Photograph of the nucleus tuberomamillaris (case 11) illustrating the chromatolysis which is characteristic of this nucleus in heat stroke.

and that which was produced experimentally in this nucleus by the injection of typhoid toxin.[1] One receives the definite impression that one is dealing here with acute changes of short duration.

In the 120 brains which have been studied to date, significant changes in the nucleus tuberomamillaris were observed only in cases of epilepsy

and heat stroke. In epilepsy there was consistent cell loss, and the cell picture, like that of the nucleus tuberis lateralis, was suggestive of chronic degenerative processes extending over a long period and continuing to the time of death, in contrast to the acute changes which were present in this nucleus in heat stroke.

The Basal Optic Ganglia (Nucleus Supraopticus) and the Substantia Grisea.—Although there was cell loss in the basal optic ganglia in 4 cases and in the substantia grisea in 1 case, it did not occur with sufficient regularity to indicate any particular significance. In the 5 control brains 96 per cent of the cells of the basal optic ganglia and 93 per cent of those in the substantia grisea were normal in appearance. In contrast to this, we observed a variable amount of chromatolysis in these nuclei in the majority of the cases of heat stroke. This chromatolysis was not sufficient in amount and did not occur with sufficient regularity to permit us to conclude that these nuclei play an important role in the production of heat stroke. On the other hand, there was sufficient deviation from the normal to make it impossible to exclude these cell groups as having any relation to this disorder. Whether the basal optic ganglia and the substantia grisea play a role in heat stroke must, for the present, remain an open question.

THEORETIC CONSIDERATIONS

The most likely interpretation which we can place on our observations is that the lateral nuclei of the tuber and a portion of the paraventricular nuclei are primarily concerned with elimination of heat. The nucleus tuberomamillaris, which is acutely affected in both experimental fever and heat stroke, is probably concerned with heat production (metabolism). If then, in cases of heat stroke the mechanisms for heat elimination are weakened, as reflected in the previous injury to the paraventricular nucleus and the lateral nucleus of the tuber, it is possible that these mechanisms break down when subjected to unusual strain such as that of adjusting to an extremely high environmental temperature. These mechanisms having broken down, the normal balance between heat production and heat elimination is destroyed. This may remove a part of the normal checks or inhibitions from the mechanisms for heat production so that the total metabolism is accelerated rather than inhibited, as would occur in the normal person. Perhaps this is reflected in the changes which occur in the nucleus tuberomamillaris in heat stroke.

SUMMARY

The nuclear groups of the hypothalamus in 13 cases of heat stroke were studied with respect to (*a*) cell counts and (*b*) pathologic alter-

ation. Comparisons were made with a series of similar observations in other cases, none of which were associated with heat stroke.

The nucleus paraventricularis in cases of heat stroke presented an average cell loss of 27 per cent; of the cells that remained an average of 77 per cent were normal. In heat stroke the large cells of this nucleus were principally affected, as compared with diabetes mellitus in which the small and medium-sized cells were principally affected.

The nucleus tuberis lateralis presented an average cell loss of 40 per cent; of the cells that remained an average of 47 per cent were normal, although there were wide individual variations in different cases. In cases used as controls, pathologic alterations frequently occurred in the cells of this nucleus, the average of normal cells being 65 per cent.

The nucleus tuberomamillaris presented no decisive alteration in cell counts. There was, however, general and constant pathologic change, with an average of only 27 per cent of cells remaining normal. The observations here were similar to those in this nucleus in experimentally produced fever; they appeared to be acute.

The basal optic ganglia (nucleus supraopticus) and the cells of the substantia grisea did not present sufficiently constant cell loss to be regarded as significant. Chromatolysis, while variable, was present in a sufficient degree to prevent elimination of these structures from consideration of their heat-regulating functions.

A chronic degenerative disease—chronic vascular sclerosis, syphilis or chronic alcoholism—was present in the 12 cases of the series in which study of all systems of the body was permitted.

As a working hypothesis, the larger cells of the more anteriorly situated nucleus paraventricularis and the cells of the nucleus tuberis lateralis are regarded as primarily concerned with the elimination of heat, while the more posteriorly situated nucleus tuberomamillaris, and probably the smaller cells of the paraventricular nucleus, are regarded as primarily concerned with the production and conservation of heat. In heat stroke the anterior nuclear groups fail to accelerate elimination of heat, apparently because of previous injury, as revealed by the diminished number of cells, while the posterior nuclear group (nucleus tuberomamillaris), with its normal number of cells but almost complete pathologic alteration, suggests intense overactivity and consequent acceleration of heat-producing mechanisms.

Regulation of temperature involves the hypothalamus, but implicates a number of cell groups rather than a single "center"; areas other than the hypothalamus may play a role.

STUDIES OF THE SPINAL FLUID IN CASES OF INJURY TO THE HEAD

EFFECTS OF DRAINAGE, ISOTONIC FLUIDS, MORPHINE AND SOLUBLE PHENOBARBITAL U. S. P. ON CEREBROSPINAL FLUID PRESSURE

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DETROIT

Alterations in cerebrospinal fluid pressure (intracranial pressure) may be studied by one of two methods: first, lumbar puncture with the needle connected with a pressure apparatus and continuous readings for several hours, or repeated punctures with pressure readings; second, in the case of patients with large defects in the skull, the use of a mechanical arrangement to record pressure changes on a tambour. In this study the first method has been used. The immediate effects of spinal fluid drainage, of fluids and of drugs have been studied by lumbar puncture with a manometer in situ for two or more hours. In some instances late effects have been studied by repeated punctures.

Investigation of the type described should be carried out with great care, for the possibilities of error are manifold. Both in the human subject and in the experimental animal there are several avenues of error. These may be tabulated as follows: 1. Psychic influences, including pain, fear and expectation, may produce changes, usually an increase, in spinal fluid pressure. 2. Movements on the part of the patient, tension and straining of the body musculature may cause increase in pressure. 3. There are physiologic alterations in the level of pressure based on heart beats and respirations. In some instances oscillations may be as much as 10 mm. with heart beats and from 40 to 50 mm. with respirations. 4. The apparatus used may not give the exact pressure reading because of capillary attraction and the bore of manometer tube; however, according to Weed, Flexner and Clark,[1] the 1 mm. bore tube used for pressure readings is probably the most accu-

From the City of Detroit Receiving Hospital and Grace Hospital.

1. Weed, L. H.; Flexner, L. B., and Clark, J. H.: Am. J. Physiol. **100**:246, 1932.

rate. 5. Fluid loss during puncture may alter readings. 6. When the method of repeated punctures is used to establish the level of pressure there may be escape of spinal fluid into the epidural space, with altered readings. 7. In some conditions, such as injury to the head, there may be a convalescing process, with normally decreasing pressure as the days follow. 8. There may be an enlarging process in the cranial cavity (such as extradural hemorrhage), which in itself may cause a progressively increasing pressure. 9. There may be repeated hemorrhages causing expected fluctuations in cerebrospinal fluid pressure. 10. In the human and in the experimental subject the use of general anesthesia may alter the picture. The effect of the anesthetic on the intracranial pressure and on the kidneys may alter the readings. One should guard against improper breathing due to improper posture. Acute flexion of the head may cause pressure on the trachea, with difficult breathing. This, as well as pressure against veins of the neck, may cause marked increase in fluid pressure.

With the avenues for error enumerated, it is apparent that studies of this type must be made with great care and that the results obtained should be sufficiently constant to justify a given conclusion. In the human subject, in whom psychic influences, movements of the body, deep breathing or straining may alter the readings, it is evident that small changes in pressure, either downward or upward, must not be considered too significant.

TECHNIC

The technic used in this study is described. A spinal puncture needle is usually inserted between the second and the third lumbar vertebra, and a water manometer of the Ayer type (2 mm. bore) is connected with the needle. The manometer is held in position on a table clamped to a tripod (fig. 1). The patient is made comfortable; the lower limbs are allowed to be extended and placed in a comfortable position. The head is supported with a pillow and placed in the anatomic position. A base line of pressure is established for fifteen or more minutes, and then the experiment is begun. In some instances the experiment lasts as long as four hours, but in the great majority readings of from two to three hours are the rule for the study of immediate effects. The average for any fifteen minutes has been recorded on the accompanying graphs. Five minute averages have been used when pertinent changes in fluid pressure justified this method of computation. In the study of changes in spinal fluid pressure as a result of forcing isotonic fluids, repeated punctures were performed to establish the pressure level on the subsequent five days, in order to note delayed effects.

MATERIAL

The material in this study is divided into three groups.

1. On 19 patients with varying degrees of injury to the head decompression was effected by drainage of the spinal fluid.

2. In 24 patients the immediate effect of intravenous injection of isotonic fluids on the cerebrospinal fluid pressure was noted. Physiologic solution of sodium chloride or 5 per cent dextrose in a physiologic solution of sodium chloride was used. To 7 patients from 1,500 to 3,000 cc. of physiologic solution of sodium chloride was administered intravenously, and the spinal fluid pressure was recorded continuously for from one and a half to three hours. To 17 patients from 1,000 to 3,000 cc. of 5 per cent dextrose in a physiologic solution of sodium chloride was given intravenously and the spinal fluid pressure recorded continuously for from one and a half to three and a half hours. To 5 patients in group 2 from 4,000 to 6,800 cc. of fluid was administered by mouth or vein for five subsequent days, and the spinal fluid pressure was recorded each day by repeated punctures.

3. The effects of morphine and soluble phenobarbital U. S. P. (sodium phenobarbital) were studied in both the patients used as controls and those with injury to the head.

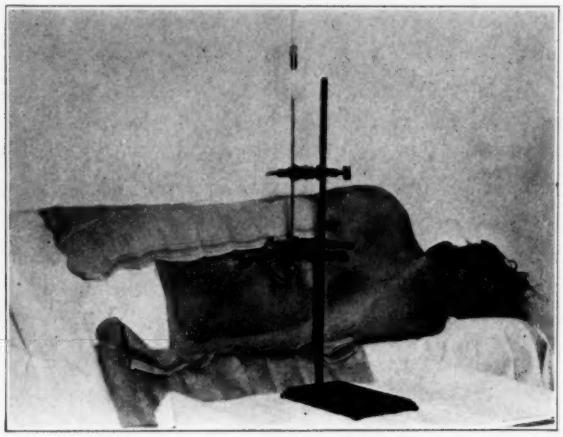

Fig. 1.—Lumbar puncture performed on a patient with fracture of the skull.

Control Group.—1. In 6 patients 5 grains (0.325 Gm.) of soluble phenobarbital was injected intramuscularly, and pressure readings were recorded for two or more hours. These persons had no complaints referable to the head.

2. In 8 patients who had no complaints referable to the head ¼ grain (0.016 Gm.) of morphine sulfate was injected intramuscularly, and pressure readings were recorded.

Group with Injuries to the Head.—1. To patients with an initial short period of unconsciousness but without fracture of the skull or bloody spinal fluid, 5 grains (0.325 Gm.) of soluble phenobarbital U. S. P. or ¼ grain (0.016 Gm.) of morphine sulfate was administered, and pressure readings were recorded for two or more hours. Ten patients were given soluble phenobarbital, and 8, ¼ grain of morphine sulfate intramuscularly.

2. To patients with varying amounts of blood in the spinal fluid and, usually, fracture of the skull, morphine sulfate, ¼ grain, or soluble phenobarbital U. S. P., 5 grains, was administered intramuscularly. Soluble phenobarbital was used in 15 cases, and morphine sulfate, ¼ grain, in 25 cases.

IMMEDIATE EFFECT OF DECOMPRESSION BY SPINAL FLUID DRAINAGE ON CEREBROSPINAL FLUID PRESSURE IN CASES OF INJURY TO THE HEAD

The effect of spinal fluid drainage on cerebrospinal fluid pressure has been the basis of excellent studies by Masserman.[2] The patients were usually seen in hospitals for mental disease. He has shown that in the great majority of patients the rapid removal of a certain amount of fluid (usually from 10 to 15 cc.), with the consequent drop of spinal

TABLE 1.—*Summary of Cases in Which a Certain Amount of Spinal Fluid Was Removed to Effect a Lowering of Pressure*

Case No.	Initial Pressure, Mm.	Lowered Pressure, Mm.	Amount of Decompression, Mm.	Fluid Removed, Cc.	Period Required to Reach Initial Pressure	Highest Pressure Reached, Mm.	Difference Between Final and Initial Pressure	Time of Observation
1	275	175	100	10	.....	230	—40	2 hr., 15 min.
2	270	150	120	10 (bloody)	45 min.	290	+20	2 hr.
3	155	90	60	20	45 min.	155	0	1 hr.
4	120	50	70	16	30 min.	160	+40	1 hr., 45 min.
5	110	50	60	10	1 hr.	130	+20	1 hr., 30 min.
6	100	50	50	15 (xanthochromic)	1 hr.	150	+50	2 hr., 15 min.
7	270	100	170	20 (xanthochromic)	1 hr., 15 min.	270	0	1 hr., 15 min.
8	60	0	60	15	2 hr.	80	+20	2 hr., 15 min.
9	180	80	100	15	.....	170	—10	2 hr., 15 min.
10	170	100	70	18	1 hr., 30 min.	170	0	2 hr.
11	300	100	200	18 (xanthochromic)	.....	220	—80	1 hr., 30 min.
12	250	100	150	13	.....	230	—20	1 hr., 30 min.
13	200	100	100	16	1 hr., 45 min.	230	+30	2 hr., 30 min.
14	200	100	100	22 (xanthochromic)	.....	150	—50	1 hr., 30 min.
15	240	100	140	22	.....	220	—20	2 hr., 30 min.
16	180	80	100	20	2 hr.	180	0	2 hr.
17	150	50	100	12 (xanthochromic)	.....	85	—65	2 hr., 15 min.
18	100	50	50	9	1 hr., 15 min.	160	+60	3 hr.
19	250	50	200	20	1 hr., 45 min.	300	+50	2 hr.

fluid pressure, is followed by a rise in pressure to a little above the initial level. In Masserman's material this was effected within about one and a half hours after the removal of fluid. In the first group of patients, table 1, the effect of rapid drainage and the eventual restoration of spinal fluid pressure were studied. As may be noted, the initial pressure in these cases ranged from 300 to 60 mm. of fluid. In 9

2. Masserman, J. H.: Cerebrospinal Hydrodynamics: Clinical Experimental Studies, Arch. Neurol. & Psychiat. **32**:523 (Sept.) 1934; Cerebrospinal Hydrodynamics: Correlations of Pressure of Cerebrospinal Fluid with Age, Blood Pressure and Pressure Index, ibid. **34**:564 (Sept.) 1935; Cerebrospinal Hydrodynamics: Effects of Intravenous Injection of Hypertonic Solutions of Dextrose, ibid. **35**:296 (Feb.) 1936.

cases the initial pressure was 200 mm. or over. The amount of decompression is given in each instance; it is noted that in 12 cases the fluid pressure rose to its initial level in an average of from thirty minutes to two hours. In 7 cases the fluid pressure remained below the initial pressure during the course of observation. In 8 cases there was a rise of cerebrospinal fluid pressure above the initial level. The highest pressure recorded was 60 mm. above the initial level. The lowest increase was 20 mm. above the initial level. It is also noted that in the great majority of cases in which the fluid pressure rose above the initial level the pressure was sustained at the new level for from a half-hour to an hour. These figures for patients with head injury are essentially the same as those obtained by Masserman for patients with no trauma to the head.

The clinical significance of these findings is important. The following conclusions may be drawn: First, a decompression by lumbar drainage in cases of injury to the head may keep the pressure lower than the initial level for several hours or longer in a certain number of cases; second, fractional drainage, in order to reduce intracranial pressure, is not followed by alarming increases in the fluid pressure in cases of no complication. Among others, Werden [3] recently has shown that daily puncture in cases of injury to the head is followed by a progressive fall in cerebrospinal fluid pressure.

The material as presented in the accompanying table is amenable to Ayala's [4] computations. The initial pressure minus the pressure obtained after decompression multiplied by the number of cubic centimeters removed gives figures ranging between 3.88 and 12. In this group of cases, although few, several of the figures below 5 did not represent the clinical picture of enlarging masses in the cranial cavity. It is our impression that in cases of injury to the head in which a combination of factors (edema and hemorrhage and lacerations of the brain) is found, Ayala's index is probably of no significant value.

IMMEDIATE AND LATE EFFECTS OF ISOTONIC FLUIDS ON CEREBROSPINAL FLUID PRESSURE IN CASES OF INJURY TO THE HEAD

Since the studies by Weed and McKibbon [5] in 1919, much interest has been shown in the effect of fluids of various concentrations administered to the human subject. Weed and McKibbon showed that hypotonic fluids administered intravenously cause a definite rise in the

3. Werden, D. H.: Drainage of Cerebrospinal Fluid in the Treatment of Acute Head Injuries, Arch. Surg. **34**:424 (March) 1937.

4. Ayala, G.: (*a*) Ztschr. f. d. ges. Neurol. u. Psychiat. **84**:42, 1923; (*b*) Monatschr. f. Psychiat. u. Neurol. **58**:65, 1925.

5. Weed, L. H., and McKibbon, P. S.: Am. J. Physiol. **48**:512, 1919.

cerebrospinal fluid pressure. Isotonic fluids were found to cause a smaller rise immediately after intravenous administration and a lowering and leveling off of pressure at or near the initial pressure thereafter. Hypertonic solutions most frequently caused a lowering of cerebrospinal fluid pressure after an initial increase. By 1922 several papers had appeared on the use of hypertonic solutions as applied to the human subject. Haden [6] used a hypertonic solution of dextrose in 2 cases of meningitis, with marked improvement of the patients' conscious state. Foley and Putnam [7] and Sachs and Malone [8] discussed the effect on the human subject of concentrated solutions of sodium chloride administered intravenously. In 1919, Ebaugh and Stevenson [9] reported the case of an epileptic patient with a decompression. Administration of from 4,000 to 8,000 cc. of fluid daily was thought to cause an increase in the intracranial pressure. McQuarrie,[10] in 1929, and Fay,[11] in 1930, discussed dehydration therapy for control of epileptic spells. Since this time dehydration has been advocated and used in treatment of head injury, both acute and chronic. In cases of the acute form it is proposed that the lowering of fluid intake reduces the intracranial pressure. Even today in some clinics, in the treatment of acute head injury, the fluid intake may be reduced to ridiculously low levels—so low that the patient is damaged in the process. It is contended that the administration of a normal amount of fluid or forcing of larger amounts would cause an increase in the intracranial pressure which, added to that already present, would damage the nervous system materially. Fremont-Smith and Merritt,[12] working with epileptic patients, noted that forcing fluids by mouth did not cause an increase in the cerebrospinal fluid pressure, as studied by repeated punctures. They also stated that in their observations the lowering of fluid intake did not reduce the cerebrospinal pressure. Their experiments were carried on for as long as seven days.

With the recent work on water balance by Coller and Maddock [13] in mind, we undertook to study the immediate effect of intravenous administration of isotonic fluids on the cerebrospinal fluid pressure. The

6. Haden, R. L.: Therapeutic Application of the Alteration of Brain Volume by the Intravenous Injection of Glucose, J. A. M. A. **73**:983 (Sept. 27) 1919.

7. Foley, F. E. B., and Putnam, T. J.: Am. J. Physiol. **53**:464, 1920.

8. Sachs, E., and Malone, J. Y.: Am. J. Physiol. **55**:277, 1921.

9. Ebaugh, F. G., and Stevenson, C. S.: Bull. Johns Hopkins Hosp. **31**: 440, 1920.

10. McQuarrie, I.: Epilepsy in Children: Relationship of Water Balance to the Occurrence of Seizures, Am. J. Dis. Child. **38**:451 (Sept.) 1929.

11. Fay, T.: J. Nerv. & Ment. Dis. **74**:481, 1930.

12. Fremont-Smith, F., and Merritt, H. H.: Influence of Variations in the Fluid Intake on Intracranial Pressure in "Epileptics," Arch. Neurol. & Psychiat. **29**:454 (March) 1933.

13. Coller, F. A., and Maddock, W. G.: Ann. Surg. **98**:952. 1933.

amounts given to some of the patients were greater than the amount usually needed. The findings are interesting in that they show that in man it is apparently difficult to upset coordinated physiologic functions maintaining the constancy of the organism (Cannon [14]). It is apparent from the data in the next few paragraphs that in the great majority of cases of acute injury to the head, forcing of fluids does not cause an increase in the cerebrospinal fluid pressure. Therefore, such patients may be given the benefit of fluids to retain a normal balance, without fear of causing increase in intracranial pressure.

In 7 cases from 1,500 to 3,000 cc. of physiologic solution of sodium chloride was administered intravenously, and the spinal fluid pressure was recorded continuously for from one and a half to three hours. In 17 cases from 1,000 to 3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride was given intravenously, and the spinal fluid pressure was recorded continuously for from one and a half to three and a half hours. In 13 cases there was no increase in the fluid pressure as a result of intravenous administration. In 6 cases an increase of 40 mm. or less was exhibited during the period of observation. In 5 cases an increase of 50 mm. or more was noted.

In 11 of the cases in which the fluid pressure did not rise above the initial level there was a lowering of the fluid pressure during the period of observation. These figures ranged from minus 10 to minus 200 mm. The lowering of the pressure was obtained not only in those in which the initial level was high but also in those in which it was comparatively low. Of interest in this group was an instance of hypotension of cerebrospinal fluid in which the injection of 1,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride was associated with a lowering of the pressure from 90 to 40 mm. of fluid. The patient was extremely ill from the beginning. The initial level of 90 mm. was out of proportion to his general condition, which was very poor. The spinal fluid was grossly bloody; in general, a patient in his condition would normally manifest a pressure of from 250 to 350 mm. of water.

In 5 cases an increase of 50 mm. or more was noted. These figures ranged from plus 50 to plus 200 mm. The patient who exhibited an increase of 200 mm. had initial hypotension of the spinal fluid. He was extremely ill, and the initial level was 90 mm. of water. This is the only frank instance of an increase in this study. It is reasonable to assume that here the intravenous administration revived the general body functions sufficiently to raise the spinal fluid pressure to a level at which it should have been under circumstances compatible with those in his case. We do not consider that the administration of the fluid in itself caused the rise in the cerebrospinal fluid pressure.

In this study of 24 cases there were 3 deaths. The patients were very ill from the beginning. The spinal fluid was bloody in each instance. In 2 cases there was hypotension of the cerebrospinal fluid, with an initial pressure of less than 100 mm. of water. In 1 of these cases the fluid pressure rose from an initial level of 90 mm. to a final level of 290 mm. of water. In the second case of hypotension of the cerebrospinal fluid the fluid pressure dropped from 90 mm. to a final pressure of 40 mm. of water. In the third case, in which the initial level was 300 mm. of water, the highest pressure recorded during three hours and fifteen minutes was 320 mm.

14. Cannon, W. B.: Physiol. Rev. **9**:399, 1929.

TABLE 2.—*Summary of Effect of Isotonic Fluids on Cerebrospinal Fluid Pressure of Twenty-Four Persons with Injury to Head*

No.	Age	Race*	Sex	Clinical Diagnosis	No. of Days Before Test	Character of Spinal Fluid	Initial Pressure, Mm.	Highest Pressure, Mm.	Final Pressure, Mm.	Blood Pressure, Mm.	Pulse Rate	Fluid Injected	Time of Observation, Hr.	Result
1	45	W	M	Cerebral concussion.....	2	Clear	170	205	205	89/50	120	1,500 cc. physiologic solution of NaCl	2	Good
2	36	W	F	Cerebral concussion.....	14	Clear	140	180	180	96/66	70	3,000 cc. physiologic solution of NaCl	1½	Good
3	44	W	M	Injury to brain.....	20	Bloody	175	215	210	130/70	90	3,000 cc. physiologic solution of NaCl	2½	Good
4	56	W	M	Skull fracture.....	4	Bloody	90	290	290	150/90	60	3,000 cc. physiologic solution of NaCl	2¼	Died
5	37	B	M	Cerebral concussion.....	3	Clear	150	210	210	100/58	75	3,000 cc. physiologic solution of NaCl	2½	Fair
6	59	W	M	Carcinoma of lung.....	30	Clear	180	185	170	108/72	80	3,000 cc. physiologic solution of NaCl	3	Good
7	55	W	M	Injury to brain.....	27	Xanthochromic	140	140	120	128/80	70	3,000 cc. physiologic solution of NaCl	3	Fair
8	25	B	M	Injury to brain.....	4	Bloody	265	340	265	136/82	60	1,000 cc. 5% dextrose†	1	Good
9	43	W	M	Injury to brain.....	2	Bloody	90	85	40	125/74	110	1,000 cc. 5% dextrose	1	Died
10	35	B	M	Injury to brain.....	12	Bloody	165	170	170	112/78	100	1,000 cc. 5% dextrose	2½	Good
11	35	B	M	Injury to brain.....	6	Bloody	240	240	175	120/75	90	1,000 cc. 5% dextrose	2¼	Good
12	42	W	M	Skull fracture.....	5	Bloody	300	320	320	125/80	60	1,000 cc. 5% dextrose	3¼	Died
13	29	W	M	Injury to brain.....	5	Clear	130	150	90	120/70	80	1,100 cc. 5% dextrose	4	Good
14	52	W	M	Skull fracture.....	4	Clear	160	160	90	108/74	80	2,000 cc. 5% dextrose	2	Good
15	75	B	M	Skull fracture.....	2	Bloody	350	350	260	110/80	70	2,000 cc. 5% dextrose	2¼	Good
16	48	W	M	Subdural hematoma.....	16	Clear	160	160	110	110/65	90	2,000 cc. 5% dextrose	2¼	Good
17	39	W	M	Skull fracture.....	7	Clear	300	300	300	100/65	75	2,000 cc. 5% dextrose	1	Good
18	20	W	M	Injury to brain.....	17	Clear	180	210	170	115/80	80	3,000 cc. 5% dextrose	3½	Good
19	32	W	M	Injury to brain.....	2	Bloody	140	180	180	120/80	130	3,000 cc. 5% dextrose	3	Good
20	58	W	M	Cerebral concussion.....	8	Clear	110	130	80	140/80	70	3,000 cc. 5% dextrose	3	Good
21	20	W	M	Injury to brain.....	6	Clear	170	230	220	125/58	110	3,000 cc. 5% dextrose	3½	Good
22	51	W	M	Skull fracture.....	6	Bloody	250	300	300	118/82	90	3,000 cc. 5% dextrose	3½	Good
23	25	W	M	Skull fracture.....	1	Bloody	400	450	200	120/70	60	3,000 cc. 5% dextrose	3	Good
24	50	W	M	Subarachnoid hemorrhage	3	Bloody	150	290	210	156/96	100	3,000 cc. 5% dextrose	1½	Good

* In this table, W indicates the white race; B, the black race.

† The dextrose was dissolved in physiologic solution of sodium chloride.

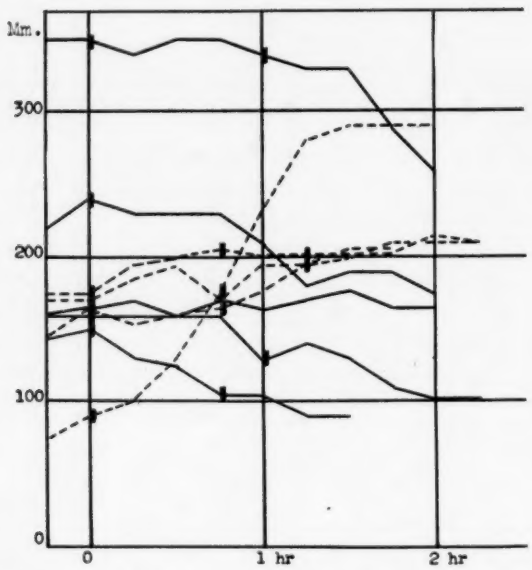

Fig. 2.—Two hour studies of the effect of intravenous administration of isotonic fluids on the cerebrospinal pressure of patients with injuries to the head.

In this chart and in the following chart, the values for physiologic solution of sodium chloride are represented by a broken line, and those for 5 per cent dextrose in physiologic solution of sodium chloride, by a solid line. In these two charts, each solid rectangle represents 1,000 cc. of fluid administered.

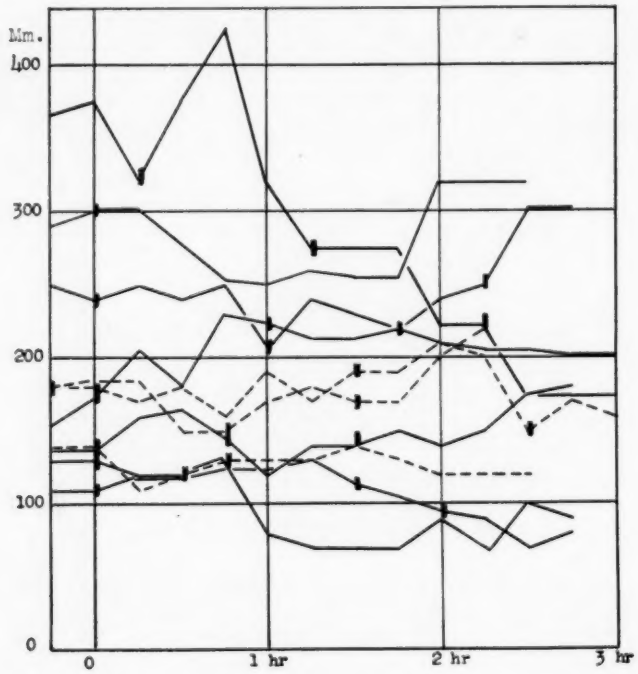

Fig. 3.—Three hour studies of the effect of intravenous administration of isotonic fluids on the cerebrospinal fluid pressure of patients with injuries to the head.

On the whole, it may be stated that isotonic fluids given intravenously in cases of injury to the head in amounts of 30 to 50 cc. per kilogram of body weight do not influence the cerebrospinal fluid pressure in the same manner as that described by Weed and his co-workers [15] in experiments on animals. In none of the cases in our series was there an immediate rise of fluid pressure after the intravenous administration. The various rises noted in this group did not follow the pattern exhibited by Weed and McKibbon. As may be seen in the graphs (figs. 2 and 3), there are several instances of a small rise during the administration of the first 1,000 cc. and no change or lowering of pressure during the administration of successive amounts.

In summary, it may be stated that the administration of from 1,000 to 3,000 cc. of isotonic fluids did not cause an increase in cerebrospinal fluid pressure in the great majority of patients. We believe that a rise or depression of the pressure of from 20 to 50 mm. must not be considered too seriously because of the influence of motion, deep breathing, sighing, fatigue and psychic factors.

In 5 cases in this group the fluid pressure was observed by daily puncture while fluids were being forced by vein and mouth. The spinal fluid pressure slowly receded to a normal level in spite of the administration of from 4,000 to 6,800 cc. of fluid per day (fig. 4). Although repeated punctures are a source of error in establishing the exact cerebrospinal fluid pressure, the readings in these cases, as well as those in 7 additional cases of uncomplicated injury to the head, prove beyond doubt that the normally expected lowering of pressure obtains in spite of ingestion of large amounts of fluid. When the eliminative organs are functioning normally the ingestion of large amounts of fluid is not contraindicated in cases of injury to the head, so far as the cerebrospinal fluid pressure is concerned.

The clinical condition of these patients following the administration of large amounts of fluid is one of improvement rather than of increased drowsiness, disorientation and restlessness. From observations on these patients, we are strongly in favor of the ingestion of a sufficient amount of fluid (from 2,500 to 3,500 cc.) in cases of severe and moderately severe injury to the head, to sustain a normal fluid balance.

EFFECT OF MORPHINE AND SOLUBLE PHENOBARBITAL U. S. P. (SODIUM PHENOBARBITAL) ON CEREBROSPINAL FLUID PRESSURE IN CASES OF INJURY TO THE HEAD [4n]

The effect of morphine and soluble phenobarbital was studied both in control cases and in cases of injury to the head. Although the work

15. Weed, L. H.: Physiol. Rev. **13**:80, 1933. Weed, L. H., and Flexner, L. B.: Am. J. Physiol. **105**:266, 1933. Weed and McKibbon.[5]

of Stevenson and his co-workers [15a] showed that morphine causes a rise in intracranial pressure, it was thought that this effect may differ according to the state of health; hence study of the effect of this drug on patients with no complaints referable to the head as well as on those with minor and serious injuries to the head was deemed advisable. We have been unable to find any reference in the literature to the effect of barbiturates on cerebrospinal fluid pressure. The material which follows has been divided into cases serving as controls and cases of injury to the head, in order to bring out the pertinent differences.

Control Cases in Which ¼ Grain (0.016 Gm.) of Morphine Sulfate Was Administered Intramuscularly.—Experiments were performed on 8 patients with no complaints referable to the head. These included 7 men and 1 woman. The

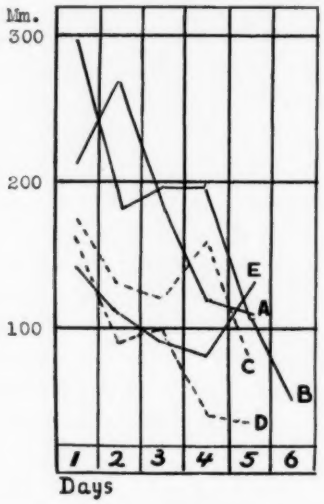

Fig. 4.—Daily records of cerebrospinal fluid pressure during forcing of fluids by mouth and by vein in patients with severe injury to the head. In a five day period, *A* received 22,650 cc.; *B*, 20,350 cc.; *C*, 25,200 cc.; *D*, 19,630 cc., and *E*, 27,650 cc.

diagnoses in these cases were: gastroenteritis, cellulitis of the hand, neuralgia, gastritis, peptic ulcer, multiple sclerosis, cerebrospinal syphilis and chronic salpingitis. The basal cerebrospinal fluid pressures were 150, 170, 160, 110, 270, 150, 215 and 150 mm. of water, respectively. The highest variations noted during a two hour study were plus 30, plus 40, plus 60, plus 35, plus 20, plus 10, plus 25 and minus 5 mm., respectively. These findings in themselves are not significant, but in view of the data in cases of injury to the head, they may be important in showing that there is a tendency of the cerebrospinal fluid pressure to rise even in normal states.

15a. Stevenson, L.; Christensen, B. E., and Wortis, B.: A. Research Nerv. & Ment. Dis., Proc. **8**:130, 1927.

The effect of certain drugs on the cerebrospinal fluid pressure was the basis of the contribution by Dixon and Halliburton.[16] They studied the influence of carbon dioxide, epinephrine, amyl nitrite and pilocarpine on the cerebrospinal fluid pressure of lower animals. Carbon dioxide, administered to an anesthetized dog, caused a definite rise in the cerebrospinal fluid pressure. Whether this was due to the asphyxiating effect of the gas, with marked muscular effort on the part of the animal, or whether the gas, per se, caused an increase in the cerebrospinal fluid pressure is a question. The increase in cerebrospinal fluid pressure caused by epinephrine was attributed by the authors to the rise in the systemic blood pressure. Wortis and Kennedy and Kennedy and

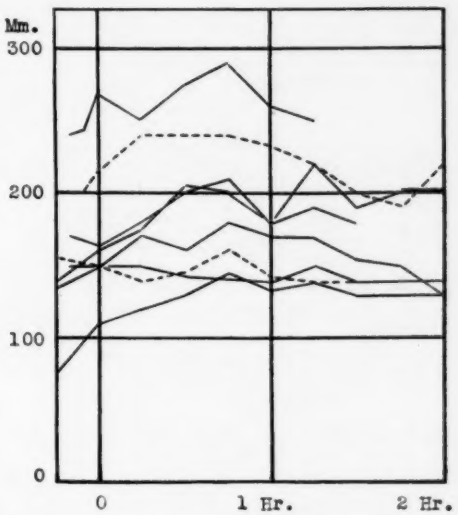

Fig. 5.—Effect of ¼ grain of morphine sulfate on the cerebrospinal fluid pressure of patients without injury to the head.

Wortis [17] studied the effect of morphine, amyl nitrite and caffeine with sodium benzoate on intracranial pressure by recording changes on a tambour attached to the patient in cases of large defects of the skull.

Control Cases in Which 5 Grains of Soluble Phenobarbital U. S. P. Was Administered Intramuscularly.—Experiments were performed on 6 patients with no complaints referable to the head. The diagnoses in these cases were: peptic ulcer, appendicitis, abdominal adhesions, syphilis, body lacerations and neuritis. The initial pressures in these cases were 125, 195, 160, 75, 245 and 100 mm. of water, respectively. The total changes in pressure during a two hour period were plus

16. Dixon, W. E., and Halliburton, W. D.: J. Physiol. **48**:128 1914.

17. Kennedy, F., and Wortis, S. B.: Modern Treatment of Increased Intracranial Pressure, J. A. M. A. **96**:1284 (April 18) 1931.

30, minus 65, minus 35, plus 35, minus 70 and plus 5 mm. of water, respectively. It may be seen that the tendency was toward a lower pressure in these cases.

Effect of Morphine Sulfate in Cases of Injury to the Head.—Cases in Which There Was an Initial Period of Unconsciousness But No Fracture of the Skull or Blood in the Spinal Fluid: In the 8 cases in this group, ¼ grain of morphine sulfate was administered intramuscularly, and the spinal fluid pressure was studied for two hours. The initial pressures in these cases were 135, 310, 170, 165, 260, 200, 100 and 225 mm., respectively. The total changes in pressure during the period of observation were plus 15, plus 90, plus 60, plus 30, plus 30, plus 50, plus 55 and plus 45 mm., respectively. The tendency toward an increase in the spinal fluid pressure was more evident in these cases.

Cases in Which There Were Varying Amounts of Blood in the Spinal Fluid and Usually Fracture of the Skull: In 11 of 25 experiments the intramuscular injection of ¼ grain of morphine sulfate caused an increase of 100 mm. or more in the spinal fluid pressure. In 6 cases there was an increase in pressure of from 50 to 100

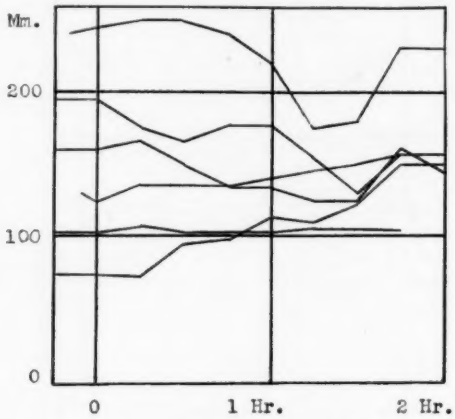

Fig. 6.—Effect of 5 grains of soluble phenobarbital U. S. P. on the cerebrospinal fluid pressure of patients without injury to the head.

mm. of water. In 6 other cases there was increase of up to 50 mm. of water. In the remaining 2 cases there were decreases in spinal fluid pressure of minus 20 and minus 35 mm., respectively. The initial pressures in these cases were 85 and 130 mm., respectively. The patient with an initial pressure of 85 mm. had a grossly bloody spinal fluid and was very ill trom the beginning. His was a frank case of hypotension of the spinal fluid.

The day after injury on which the test is performed seems significant in that in a case of severe injury to the head the sooner the patient is given morphine the more readily he will react. In 12 cases morphine was administered within the first five days after the accident. In this group tremendous increases were seen frequently, as shown in table 3, and the difference becomes evident when the results in cases in which the drug was given ten days or more after the injury are compared. However, an occasional instance of a large increase in fluid pressure

TABLE 3.—*Cerebrospinal Fluid Pressure Before and After Administration of ¼ Grain Morphine Sulfate to Twenty-Five Patients with Severe Injury to the Head*

No.	Age, Yr.	Race*	Sex	Clinical Diagnosis	No. of Days Between Test and Injury	Spinal Fluid	Initial Pressure, Mm.	Highest Variation, Mm.	Total Change in Pressure, Mm.	Blood Pressure, Mm.	Pulse Rate	Operation	Result
1	39	W	M	Laceration of brain (left subdural hematoma)	2	Very bloody	320	650	+330	130/ 90	80	.....	Transferred
2	50	W	M	Laceration of brain.....	7	Very bloody	390	650	+260	180/138	130	.....	Died
3	50	W	M	Laceration of brain.....	2	Very bloody	320	485	+165	180/115	128	.....	Died
4	22	W	M	Fractured skull.....	21	1st day bloody, 270 mm.; 3d day xanthochromic, 110 mm.	230	270	+ 40	130/ 70	75	.....	Good
5	39	B	M	Fractured skull.....	10	Bloody	230	330	+100	130/ 80	75	.....	Good
6	42	W	M	Fractured skull.....	2	Clear	155	225	+ 70	134/ 90	90	.....	Good
7	56	W	M	Fractured skull.....	3	Bloody	250	375	+125	180/ 82	78	.....	Transferred
8	44	B	M	Compound depressed skull fracture	11	Clear	150	200	+ 50	140/100	80	Elevation of depression	Good
9	61	W	M	Fractured skull.....	3	Clear	135	200	+ 65	124/ 74	80	.....	Good
10	52	W	M	Laceration of brain.....	3	Bloody	200	360	+160	122/ 84	80	.....	Good
11	41	W	M	Fractured skull.....	21	2d day b'oody; 3d day less bloody; 21st day c.ear	60	65	+ 5	130/ 60	60	.....	Good
12	70	W	M	Fractured skull.....	4	Clear	110	150	+ 40	100/ 58	60	.....	Good
13	50	W	M	Right arteriovenous aneurysm, carotid and cavernous sinus	20	Clear	190	235	+ 45	116/ 70	80	Ligation of right carotid artery	Died
14	46	W	M	Fractured skull.....	19	Clear	150	195	+ 45	102/ 74	98	.....	Good
15	56	W	M	Fractured skull.....	8	Clear	120	170	+ 50	170/128	80	.....	Good
16	56	W	M	Laceration of brain.....	2	Bloody	85	65	— 20	170/110	95	.....	Died
17	29	W	M	Laceration of brain.....	9	Slightly bloody	150	265	+115	116/ 78	90	.....	Good
18	52	W	M	Fractured skull.....	10	Clear	260	420	+160	110/ 85	...	.....	Good
19	37	B	M	Fractured skull.....	5	Clear	330	600	+270	130/ 75	70	.....	Good
20	37	B	M	Fractured skull.....	7 weeks	Clear	260	340	+ 80	124/ 70	80	.....	Good
21	72	W	M	Fractured skull.....	2	Bloody	115	230	+115	190/102	70	.....	Good
22	25	B	M	Laceration of brain.....	4	Bloody	265	280	+ 15	136/ 82	60	.....	Good
23	25	B	M	Laceration of brain.....	9	Clear	315	375	+ 60	126/ 76	90	.....	Good
24	57	W	M	Laceration of brain.....	2	Bloody	130	95	— 35	190/100	94	.....	Good
25	35	B	M	Laceration of brain; possible subdural hematoma; fractured skull	6	Bloody	160	260	+100	162/ 78	100	.....	Good

* In this table, W indicates the white race; B, the black race.

occurs; in case 18, for example, the drug was given on the tenth day, and the spinal fluid pressure rose from 260 to 420 mm.—a difference of plus 160 mm. That the day after injury on which morphine is administered is significant is also proved in 2 cases in this group in which on subsequent administration of the drug there were increases in pressure of much smaller amounts than at the first determinations.

In 44 per cent of cases in the entire group a definite and irrefutable increase in cerebrospinal fluid pressure followed the administration of morphine. In this group of 11 cases the increase in cerebro-

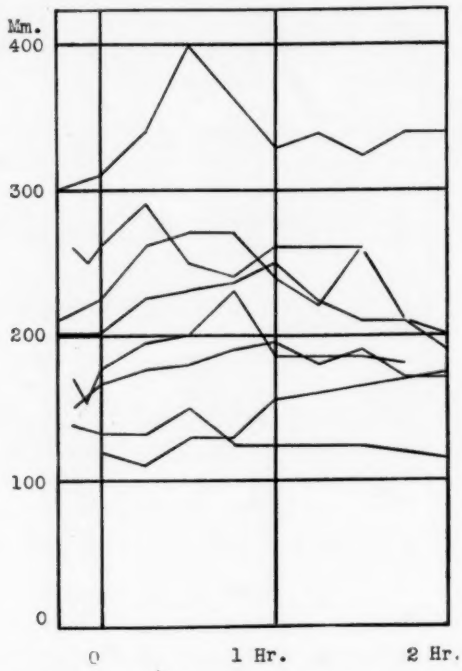

Fig. 7.—Effect of ¼ grain of morphine sulfate on the cerebrospinal fluid pressure of patients with cerebral concussion.

spinal fluid pressure ranged between plus 100 and plus 230 mm. of water. The increase in pressure invariably occurred within the first fifteen to forty-five minutes of the observation. The spinal fluid was bloody in all but 2 cases. The observations were made within the first ten days after admission. The initial pressure was frequently high, but not always. An initial pressure of 200 mm. of water or less was seen in 5 cases. In this group of 11 cases there were 2 deaths.

In general, the more severe the injury to the head the more prompt was the rise in cerebrospinal fluid pressure. The reason for such a rise is obscure. It is evident from the preceding findings that patients with

no injury to the head and those with very slight injury are not influenced by morphine to the same degree as those with severe injury. This difference in reaction suggests the possibility that the organism is capable of offsetting the effects of morphine under normal circumstances. In the normal person with no or with slight injury to the head

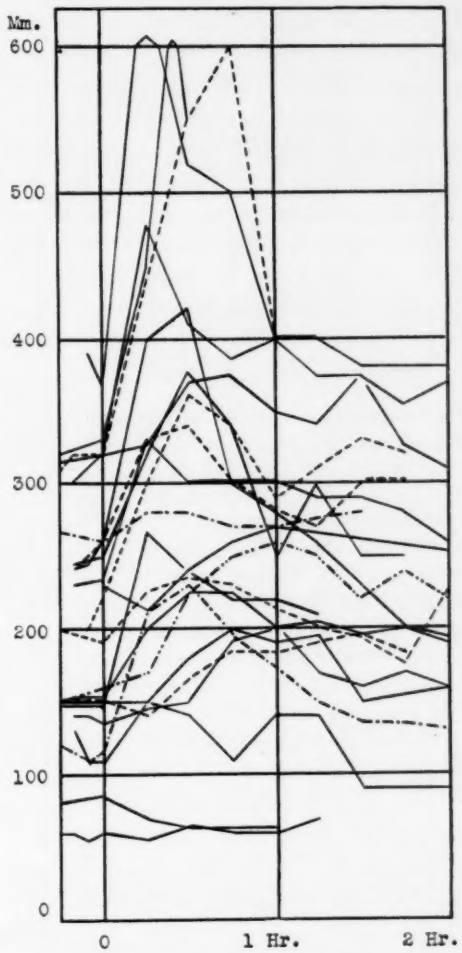

Fig. 8.—Effect of ¼ grain of morphine sulfate on the cerebrospinal fluid pressure of patients with bloody spinal fluid and/or fracture of the skull.

the principle of homeostasis expounded by Cannon is apparently in operation; that is, in such a case the coordinated physiologic actions maintain the constancy of the organism. However, the additional load of a severe injury to the head cannot be coped with. In cases of such injury the administration of morphine cannot be discounted as easily as in those in

which there is minor or no injury to the head. In cases of severe injury, coordinated physiologic action apparently cannot maintain the constancy of the organism when morphine is administered, hence the tremendous rise in cerebrospinal fluid pressure. What does the patient with severe head injury have that the patient with no or with slight injury does not possess? The patient with severe head injury suffers from edema of the brain, contusions and hemorrhages in the intracranial contents, derangement of intracranial circulation or a combination of all these. Does morphine cause a venous stasis which, together with the deranged circulatory mechanism of the head, is responsible for the rise in cerebrospinal fluid pressure? Does morphine cause further edema of the brain, in addition to that already in existence? Does morphine produce a vasoconstrictor action in the splanchnic area, with consequent edema and congestion of the brain? Another possible explanation for marked changes in cases of severe injury to the head is that with the presence of edema, contusions and hemorrhages there is already a state of partial anoxia, to which the addition of further anoxia by morphine may increase the already existent high intracranial pressure.

Effect of Soluble Phenobarbital U. S. P. in Cases of Injury to the Head.—Cases in Which There Was Initial Period of Unconsciousness But No Fracture of the Skull or Blood in the Spinal Fluid: In 10 cases 5 grains of soluble phenobarbital was injected intramuscularly. The initial pressures in these cases were 190, 195, 255, 135, 180, 110, 145, 200, 110 and 210 mm., respectively. The total changes in pressure in these cases were plus 70, minus 10, plus 45, plus 25, plus 60, plus 50, plus 15, plus 40 and plus 10 mm., respectively. There was a tendency toward some increase in 8 cases, and this was a little less evident than that following morphine. In 2 cases there was a decrease in pressure.

Cases in Which There Were Varying Amounts of Blood in the Spinal Fluid and Usually Fracture of the Skull: In 15 experiments the results were practically the same as those in the preceding group. The reaction to the drug in this group differed greatly from that to morphine. In 4 cases there was a decrease in pressure. In 7 cases the increase in pressure was less than 50 mm. In the remaining 4 cases the increase in pressure was between 50 and 90 mm. of water.

Soluble phenobarbital has been found fairly effective in quieting the disoriented patient with an injury to the head, although it cannot be compared in this respect with morphine sulfate. The action of other sedatives and narcotics is at present in process of investigation to discover the most effective and least harmful agent.

CONCLUSIONS

1. A sudden drop in spinal fluid pressure caused by rapid drainage of fluid by lumbar puncture was followed by a slow rise, reaching the initial level in about one-half the cases. In a certain number of cases the pressure rose from 10 to 60 mm. above the initial level. No

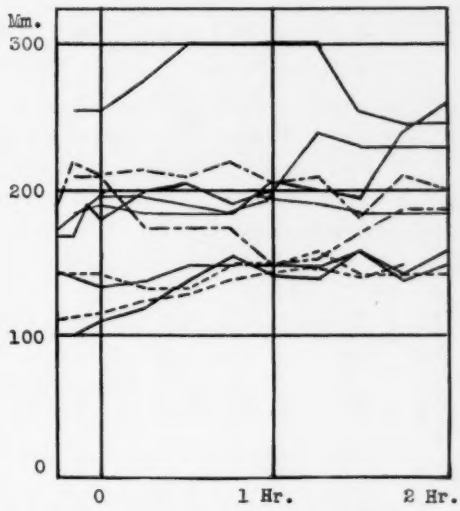

Fig. 9.—Effect of intramuscular injection of 5 grains of soluble phenobarbital U. S. P. on the cerebrospinal fluid pressure of patients with cerebral concussion.

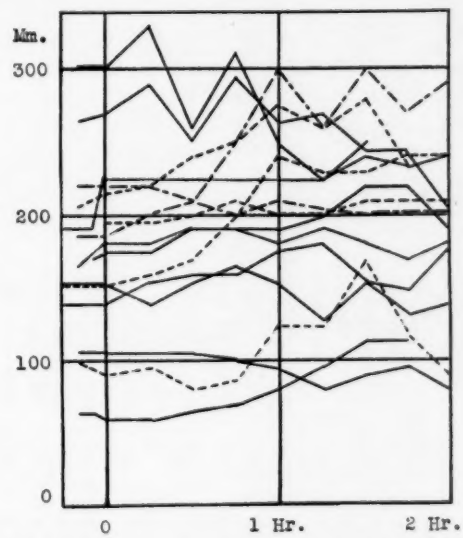

Fig. 10.—Effect of 5 grains of soluble phenobarbital U. S. P., injected intramuscularly, on the cerebrospinal fluid pressure of patients with fracture of the skull.

TABLE 4.—*Effect of Intramuscular Administration of 5 Grains of Soluble Phenobarbital U. S. P. on Cerebrospinal Fluid Pressure of Patients with Skull Fracture or Bloody Fluid*

No.	Age, Yr.	Race*	Sex	Clinical Diagnosis	No. of Days Between Test and Injury	Spinal Fluid	Initial Pressure, Mm.	Highest Pressure, Mm.	Total Change in Pressure, Mm.	Blood Pressure, Mm.	Pulse Rate	Result
1	49	W	M	Fractured skull	5	Clear, 190 mm.	225	240	+15	112/ 78	70	Good
2	40	W	M	Fractured skull	3	Clear, 140 mm.	140	180	+40	124/ 80	80	Good
3	11	W	M	Fractured skull	1	Clear, 165 mm.	155	130	−25	95/ 65	90	Good
4	38	W	M	Fractured skull	4	Clear, 170 mm.	175	220	+45	130/ 80	85	Good
5	28	W	F	Fractured skull	2	Slightly bloody, 300 mm.	300	225	−75	110/ 70	85	Good
6	55	B	M	Fractured skull	8	Clear, 105 mm.	105	80	−25	120/100	80	Good
7	55	B	M	Fractured skull	1	Clear, 65 mm.	65	115	+50	140/ 90	100	Good
8	57	W	M	Injury to brain	1	Bloody, 270 mm.	270	205	−65	210/130	80	Good
9	25	B	M	Injury to brain	1	Slightly bloody, 205 mm.	215	275	+65	126/ 76	90	Good
10	50	W	M	Injury to brain	5	Slightly bloody, 220 mm.	220	300	+80	144/110	110	Died
11	39	B	M	Fractured skull	11	Clear, 160 mm.	195	210	+15	118/ 88	70	Good
12	40	W	M	Fractured skull	2	Clear, 185 mm.	185	210	+25	145/ 85	80	Good
13	14	W	F	Fractured skull	5	Clear, 250 mm.	250	340	+90	100/ 70	90	Good
14	35	B	M	Injury to brain	7	Bloody, 180 mm.	180	190	+10	110/ 70	90	Good
15	43	W	M	Injury to brain; possible epidural hemorrhage	2	Bloody, 90 mm.; 40,000 red blood cells	90	170	+80	125/ 74	110	Died

* In this table, W indicates the white race; B, the black race.

alarmingly high pressures were recorded after spinal fluid drainage in these cases of injury to the head. The use of lumbar puncture as a decompressive agent in selected cases of injury to the head is worth while. Ayala's index, computed from figures obtained in this phase of the study, was not helpful in the diagnosis of expanding lesions.

2. The intravenous administration of isotonic fluids did not cause an increase in the cerebrospinal fluid pressure in the great majority of cases. The delayed effects of the administration of large amounts of fluids by mouth and by vein were not unusual, and the cerebrospinal fluid pressure in this group receded to normal levels, in spite of forcing fluids. It is believed that a sufficient amount of fluid can be given in a case of moderately severe injury to the head to obtain a normal fluid balance without jeopardizing the patient or causing an increase in the intracranial tension. Patients with severe injury to the head, who remain unconscious for days, should be given from 2,500 to 3,500 cc. of fluid by vein, under the skin or through a stomach tube.

3. The effect of morphine on cerebrospinal fluid pressure was found to differ in cases of no or slight injury to the head from that in cases of severe injury. In patients with no or slight injury there was little increase in pressure; in those with severe injury the cerebrospinal fluid pressure increased conspicuously after administration of morphine. Masking of symptoms and depression of respiration are not the only contraindications to the use of morphine in cases of injury to the head. In the majority of cases of severe injury morphine causes an undeniable increase in cerebrospinal fluid pressure, and its use is dangerous.

4. Soluble phenobarbital U. S. P. (sodium phenobarbital) did not cause marked variation of the cerebrospinal fluid pressure in patients with severe injury to the head.

5. In the management of severe head injury with disorientation and restlessness, the use of narcotics and sedatives should be minimal. Certainly, morphine should hardly ever be used for this purpose, for in a certain number of cases it will cause a tremendous rise in the cerebrospinal fluid pressure, which may endanger the life of the patient.

Case Reports

EFFECT OF BENZEDRINE SULFATE IN TREATMENT OF PSYCHOSIS WITH POSTENCEPHALITIC PARKINSONISM

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During the last few years considerable study has been made of the clinical effect of benzedrine sulfate in various physiologic and pathologic conditions.[1] Benzedrine sulfate, a sympathomimetic drug, has lately been advocated for use in the treatment of postencephalitic parkinsonism.

In the past it had been routine practice at the Hudson County Hospital to treat patients suffering from psychosis with chronic encephalitis by means of large doses of atropine sulfate or scopolamine hydrobromide. Atropine sulfate was given in increasing doses, starting with 1 drop of a 0.5 per cent solution three times a day, as suggested by Stemplinger [2] and others,[3] and increasing the dose gradually to 12 or 15 drops three times a day, according to individual tolerance. Scopolamine hydrobromide was prescribed in doses of $\frac{1}{100}$ grain (0.6 mg.) three times a day.

In deciding to give benzedrine a trial, we were particularly interested to learn: (1) its effect on the structure of the psychosis and psychotic manifestations; (2) the maximum duration of administration, as required for chronic institutionalized patients, without severe untoward effects, and (3) its advantages over the drugs, such as atropine, scopolamine and stramonium, used in the past in treatment of postencephalitic parkinsonism.

EFFECT OF BENZEDRINE SULFATE ON THE PSYCHOTIC PICTURE OF POSTENCEPHALITIC PARKINSONISM

In reviewing the literature relative to the influence of benzedrine sulfate on the structure of psychosis in general, I may quote Schube,

Read at the twenty-eighth annual meeting of the American Psychopathological Association, Atlantic City, N. J., May 4, 1938.

1. Myerson, A.: Effect of Benzedrine Sulfate on Mood and Fatigue in Normal and in Neurotic Persons, Arch. Neurol. & Psychiat. **36**:816 (Oct.) 1936. Peoples, S. A., and Guttman, E.: Hypertension Produced with Benzedrine, Lancet **1**:1107 (May 16) 1936.

2. Stemplinger, F.: Zur Therapie des postenzephalitischen Parkinsonismus, München. med. Wchnschr. **77**:1926 (Nov. 7) 1930.

3. Adams, F. M., and Hays, P. L.: The Atropine Treatment of the Postencephalitic Parkinsonian Syndrome, Am. J. Psychiat. **91**:151 (July) 1934.

McManamy, Trapp and Myerson,[4] who studied the effects of benzedrine on patients with certain major psychoses and reached the following conclusion:

> There was no improvement in any case. In 15 of the 80 cases studied there was temporary accentuation of the psychosis. Benzedrine sulphate was of no value in the alleviation of the psychoses in the cases studied. . . . In one individual there resulted a definite persistent suicidal drive.

Davidoff,[5] in studying the effect of benzedrine sulfate on self-absorbed patients, said:

> In no case did benzedrine profoundly alter the structure of the psychosis, although it did accelerate a definite symptomatic improvement in six cases of the 30; of the 22 catatonics, only three showed noteworthy improvement from the standpoint of eligibility for parole. This may be said to differ only slightly, or not at all, from the improvement noted in the ordinary spontaneous fluctuations and remissions observed in the course of catatonic states. . . . It did not alter the total personality reaction in any case.

Wilbur, MacLean and Allen [6] pointed out:

> It should be particularly emphasized that benzedrine is a stimulant and therefore that it probably does not fundamentally and permanently alter a psychotic disorder or a state of chronic exhaustion or neurosis.

Material and Method.—The group studied by me consisted of 8 patients, 4 men and 4 women; all the patients were hospitalized and could therefore be closely observed. All the patients had a condition diagnosed as psychosis with post-encephalitic parkinsonism and a definite history of epidemic encephalitis some time previous to admission to the hospital. The patients had been in the hospital from eight months in 1 case, to four and one-half years, in another, when treatment with benzedrine sulfate was started. They lived at the hospital under the same routine and remained in the same wards throughout the period of treatment; no changes of any sort were introduced, to avoid psychologic factors that might influence or complicate the situation.

Tablets of benzedrine sulfate were administered continuously for four months. During the first two weeks each patient received 5 mg. of the drug at 8 a. m. and again at noon. The dose was later increased to 10 mg. twice a day; at no time was benzedrine given after midday. During the four months some of the patients received a total of 2,200 mg. of benzedrine sulfate. At the end of the fourth month the patients were given placebos resembling the tablets of benzedrine.

Results.—During the first week or two of the treatment, some of the patients, previously drowsy and apathetic, showed slight elevation in mood and others even mild euphoria; this was not lasting, however,

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4. Schube, P. G.; McManamy, M. C.; Trapp, C. E., and Myerson, A.: The Effect of Benzedrine Sulphate on Certain Abnormal Mental States, Am. J. Psychiat. **94**:27 (July) 1937.

5. Davidoff, E.: A Clinical Study of the Effect of Benzedrine Therapy on Self-Absorbed Patients, Psychiatric Quart. **10**:652 (Oct.) 1936.

6. Wilbur, D. L.; MacLean, A. R., and Allen, E. V.: Clinical Observations on the Effect of Benzedrine Sulphate: Study of Patients with States of Chronic Exhaustion, Depression and Psychoneurosis, J. A. M. A. **109**:549 (Aug. 21) 1937.

and after the third week they lapsed into the former state of apathy. One patient (case 2), after slight improvement, became disturbed, confused and panicky and jumped down a laundry chute. When questioned later, she was so hazy about this experience that she could not explain whether her intention was to escape or to commit suicide. Another patient (case 3) appeared brighter at the beginning of the benzedrine treatment, but it was noticed that the same reaction occurred whenever her husband visited her. Lately he had neglected the visits; when he failed to appear on several days as she expected, she became depressed and dejected in spite of the benzedrine.

It must be borne in mind that accurate evaluation of the changes due to any therapeutic effort is extremely difficult in the case of psychotic patients, who might react to many incidental factors not connected directly with the therapy instituted. Even though all the patients in this study lived at the hospital supposedly under the same conditions and subject to the same routine, a visit from a member of the family to one patient or the failure of an expected visit to another made considerable difference in the mood of the patient and influenced and upset, in many respects, the observations of the physician as to the progress made.

It was my general impression that while there was occasional elevation of mood in some patients, it was by no means constant and that no significant change was noted in the structure of the psychosis in any of the patients during the entire four month period of treatment. Certainly, none of them improved enough to be considered eligible for parole.

UNTOWARD EFFECTS

I desired particularly to determine what ill effects, if any, might result from taking benzedrine sulfate over a prolonged period, as is often required in the treatment of institutionalized patients with postencephalitic parkinsonism. Several clinicians have sounded warnings against too prolonged and indiscriminate use of the drug. Davies [7] reported a case of acute aplastic anemia following self administration of benzedrine.

> The total amount taken was 190 mg. in the course of nineteen days. Severe cardiovascular collapse occurred the day after the last dose was taken. Gradual recovery ensued, with restoration to normal health.

Apfelberg [8] described a case of poisoning with benzedrine sulfate with ultimate recovery in a psychoneurotic person who took 140 mg. of the drug in one dose. Yet Davidoff and Reifenstein [9] reported that they had given 200 mg. in one day to a patient without severe ill

7. Davies, I. J.: Benzedrine: A Review of Its Toxic Effect with the Report of a Severe Case of Anaemia Following Its Use, Brit. M. J. **2**:615 (Sept. 25) 1937.

8. Apfelberg, B.: A Case of Benzedrine Sulfate Poisoning, J. A. M. A. **110**: 575 (Feb. 19) 1938.

9. Davidoff, E., and Reifenstein, E. C., Jr.: The Stimulating Action of Benzedrine Sulphate: Comparative Study of the Responses of Normal Persons and of Depressed Patients, J. A. M. A. **108**:1770 (May 22) 1937.

effects, while Solomon and his associates [10] gave 160 mg. of benzedrine sulfate daily for three weeks without any complications.

Other workers have reported numerous unfavorable reactions, ranging from mild irritability and anxiety to panicky states, sometimes cardiac collapse and a rise in the systolic blood pressure of over 100 mm., after taking only 20 mg. of the drug.

When the small group of postencephalitic patients was selected for this study, those with heart disease, marked arteriosclerosis and hypertension were excluded. None of the patients suffered any severe ill effects during the four month period, except for the confused, panicky episode in case 2, already mentioned. In no case was there an increase of more than 25 mm. in the systolic blood pressure or of more than 23 mm. in the diastolic pressure. One patient (case 6) showed a drop of 20 mm. in the systolic blood pressure at the end of the fourth month. None experienced any cardiac difficulty as far as could be observed. There was no constant variation in weight during the entire period of treatment: Three patients lost weight; 2 gained some weight, and the weight of 3 remained unchanged. One undernourished patient (case 1) weighed 94 pounds (42.6 Kg.) at the beginning of the treatment and 86 pounds (39 Kg.) at the end, a loss of 8 pounds (3.6 Kg.), which was undesirable in her case. When benzedrine sulfate was discontinued she began to regain weight.

Blood counts were made throughout the treatment; again, except for a slight rise in the number of red cells in 2 cases, nothing significantly constant was noted.

It seems that although some persons may have individual idiosyncrasies to benzedrine sulfate, prolonged administration of the drug in relatively small doses is fairly safe, provided, of course, that each patient undergoes careful physical examination at the beginning of the treatment and remains under a physician's supervision, or reports for a check-up at frequent intervals, throughout the period of treatment.

COMPARISON OF BENZEDRINE SULFATE WITH ATROPINE, SCOPOLAMINE AND STRAMONIUM IN TREATMENT OF PARKINSONISM

The question arises as to whether anything is to be gained by substituting benzedrine sulfate for atropine or scopolamine in the symptomatic management of patients with parkinsonism.

Atropine established its usefulness in the treatment of parkinsonism by controlling, to a certain extent, tremors, rigidity, disturbances in gait and other motor phenomena, and it has been found particularly effective in diminishing such distressing vegetative disturbances as continuous drooling of saliva. The same applies to scopolamine and stramonium.

Benzedrine has been suggested by some research workers because of its elevating effect on mood, most postencephalitic adult patients

10. Solomon, P.; Mitchell, R. S., and Prinzmetal, M.: The Use of Benzedrine Sulphate in Postencephalitic Parkinson's Disease, J. A. M. A. **108**:1765 (May 22) 1937.

being drowsy, apathetic, retarded and often emotionally unstable, and because of its alleviation of oculogyric crises.[10]

There was comparatively little difficulty in maintaining large doses of atropine for a long period. If the patients complained of dryness of the throat or flushing of the face administration of atropine was usually temporarily discontinued or the dose reduced.

When benzedrine was substituted for atropine some patients again complained of salivation, although they had been relatively free from the distressing symptom for a long time, while receiving atropine.

Two patients suffered from attacks of oculogyric crises; in both cases the attacks diminished in severity and frequency while the patients were receiving benzedrine.

Recently, several investigators [11] have found that patients with parkinsonism do best under treatment with benzedrine combined with atropine or scopolamine. I am now testing this method of treatment, but am not yet in a position to report any definite results.

It seems possible that patients particularly distressed by salivation will do best with atropine, while others suffering from oculogyric crises may be relieved by benzedrine or a combination of the two. Benzedrine should not be prescribed for extremely undernourished patients. The therapy selected should be adapted to the individual patient according to the predominating symptoms, since at present the whole treatment must, unfortunately, remain on a purely symptomatic basis.

REPORT OF CASES

CASE 1.—A. F., a single woman aged 28, was admitted to the hospital in 1933 with the diagnosis of psychosis with epidemic encephalitis, the acute attack having occurred in 1922. She was irritable, irascible and emotionally unstable, but was able to engage in gainful occupation until November 1932, when she lost her position and her mental condition became aggravated. At the hospital she cried on the slightest provocation, imagined people talked about her and appeared to be constantly annoyed by the most trivial things. Neurologically, she presented occasional diplopia, unequal pupils, salivation, festination, masklike facial expression, rigidity of the muscles of the face and extremities and pill-rolling tremors of the fingers of the left hand. Large doses of atropine controlled the rigidity and tremors to some extent. She was paroled six months after admission, but was unable to make a satisfactory adjustment and was readmitted in 1936. On Sept. 20, 1937 treatment was started with benzedrine sulfate, 5 mg. twice a day. She showed slight symptomatic improvement and some elevation of mood for about a month. After the sixth week of administration of the drug the dose was increased to 10 mg. twice a day, but the improvement did not continue. She complained that the nurses in the ward did not treat her as well as other patients, although she said she did everything possible on her part to conform with hospital regulations. A week later she had a marked episode of excitement, and in a fit of anger smashed a glass jar against a wall. After being treated with benzedrine continually for four months she was given placebo tablets and was unable to tell the difference. She lost 8 pounds (3.6 Kg.) in weight while under treatment with benzedrine. The blood pressure before the benzedrine treatment was 114 systolic

11. Finkelman, I., and Shapiro, L. B.: Benzedrine Sulphate and Atropine in the Treatment of Chronic Encephalitis, J. A. M. A. **109**:344 (July 31) 1937. Solomon, Mitchell and Prinzmetal.[10]

and 65 diastolic, and the highest pressure after treatment was 130 systolic and 86 diastolic. The weight before treatment was 94 pounds (42.6 Kg.), and after treatment, 86 pounds (39 Kg.).

CASE 2.—E. K., a single woman aged 24, was admitted in 1935 with a history of encephalitis at the age of 7 years and of diplopia, drowsiness and hypersomnia for four years prior to admission. On admission she showed tremor of both hands, pill-rolling movement in the left hand, rigidity of the muscles of the face and of both lower and upper extremities, festination, sluggish pupillary reaction and some evidence of ophthalmoparesis. She was emotionally unstable, subject to outbursts of excitement and generally mischievous, erratic and sexually promiscuous. While at the hospital she escaped on two occasions and was returned to the hospital by her family. She was treated at various times at the hospital with atropine, tincture of stramonium and scopolamine. On Sept. 20, 1937 administration of benzedrine sulfate, 5 mg. at 8 a. m. and again at noon, was started. She showed slight symptomatic improvement, especially diminution in tremor and rigidity; two weeks later the dose was increased to 10 mg. of benzedrine sulfate twice a day. Three days later she became disturbed, confused and panicky and, while in a state of confusion, jumped down a laundry chute, receiving, fortunately, only superficial abrasions. When questioned, she was unable to explain whether her intention was to escape or to commit suicide, and she still states that she did not know what she was doing. After this incident the treatment with benzedrine was discontinued. She now receives atropine and adjusts fairly well as an institutionalized patient.

CASE 3.—A. C., a married woman aged 29, who was admitted to the hospital in 1933, had been treated at the Neurological Institute of New York in 1928, where her condition was diagnosed as epidemic encephalitis with parkinsonism. In 1932 there developed persistent ideas of jealousy; she accused her husband of going out with other women, and later expressed definite paranoid delusions; she imagined that the druggist was putting poison in the medicine that was prescribed for her nervous condition. On admission she was emotionally unstable, cried much and thought her husband intended to kill her. There was no apparent intellectual impairment. Physically, she showed a typical picture of parkinsonism. She had been receiving stramonium before admission, and while at the hospital she was treated with large doses of atropine and scopolamine. On Sept. 20, 1937 treatment was started with benzedrine sulfate, 5 mg. twice a day. She seemed to become more stable emotionally and less depressed; her husband had become negligent in visiting her, and when he came one day she looked much brighter and happier. It was difficult to say whether the husband's visit or the benzedrine made her feel better; on the following Sunday, however, when the husband failed to come, although he had promised to do so, she appeared depressed and dejected in spite of the benzedrine. It was generally noted by all workers, physicians and nurses that her husband's visits elevated her mood to a much greater degree than the medication. Later she was treated with 10 mg. of benzedrine sulfate twice a day, with little success. Objectively, improvement was not marked; subjectively, she insisted that she felt fine and that the new medicine did her much good, even when she was given a placebo. The blood pressure before treatment with benzedrine was 126 systolic and 86 diastolic; the greatest elevation after treatment was to 130 systolic and 88 diastolic.

CASE 4.—G. J., a man aged 48, was committed to the hospital in 1934 with the history of a severe attack of influenza in 1918. A year before his admission to the hospital there developed a parkinsonian syndrome, with disturbances in sleep,

insomnia at night and hypersomnia in the daytime. He was committed because of attempted suicide by hanging; while at the hospital he often expressed suicidal thoughts. He had many somatic delusions, insisting that two thirds of his body was dead and only one-third was alive and that he had not slept a minute in the last two years. He suffered from episodes of depression, with emotional instability, and had many morbid ideas. Constant drooling of saliva was a particularly distressing symptom, but this was well controlled with large doses of atropine sulfate. During the first two weeks in which he was given benzedrine sulfate he looked brighter and walked with less difficulty, so that the nurses and physicians who observed him thought that he showed decided improvement, although he continued to repeat that his body was two-thirds dead and to express the same morbid ideas. In general there was not the slightest change in the structure of his psychosis during the four months he was treated with benzedrine, and salivation again became a distressing symptom. The original improvement in diminution of tremor and rigidity was not sustained. The patient is now being treated with scopolamine hydrobromide, 1/100 grain (0.6 mg.) three times a day, and phenobarbital, 1 grain (0.65 Gm.), at 8 p. m., with which he seems to do best. The blood pressure before treatment was 112 systolic and 70 diastolic; the greatest pressure after treatment was 128 systolic and 86 diastolic. The weight was 145 pounds (65.8 Kg.) before treatment and 145¼ pounds (65.9 Kg.) after treatment.

Case 5.—P. W., a single man aged 29, was transferred from another institution in January 1937, where his condition was diagnosed as psychosis with epidemic encephalitis, Parkinson's syndrome. He had encephalitis in 1928, after which he noticed that his eyes turned outward and his left arm became rigid. However, the psychotic symptoms did not become marked until 1936, when he required hospitalization; at that time, while in a fit of rage, he tried to choke his mother and attacked his father. He showed marked emotional instability, believed the whole world was against him and at one time thought a girl wanted to poison him. He had been having oculogyric crises about twice a week. He presented a picture typical of postencephalitic parkinsonism, with monotonous speech, masklike facial expression, some ophthalmoparesis, strabismus, a history of diplopia in the past, salivation and tremor of both hands, more pronounced on the left, with a tendency to pill-rolling movement. After the routine treatment with atropine, on Sept. 20, 1937, benzedrine sulfate, 5 mg. twice a day, was prescribed. There was slight diminution in the severity of the oculogyric crises, and the attacks occurred only once a week, instead of twice, as previously. He was then given placebo tablets for two weeks, and during this period he had four attacks of oculogyric crises. Otherwise, his condition remained unchanged. The psychotic picture was not influenced in any way. The blood pressure before he received benzedrine was 102 systolic and 72 diastolic, and the greatest pressure after treatment was 120 systolic and 80 diastolic. The weight before treatment was 132¼ pounds (60 Kg.), and that after treatment, 134 pounds (60.8 Kg.).

Case 6.—A. S., a woman aged 54, had epidemic encephalitis three months before admission to the hospital. On admission in 1931 she was confused, drowsy and sleepy, had many memory defects and showed marked clouding of the sensorium. Neurologically, she had diplopia, limitation of ocular movements, defective conjugate deviation, masked facial expression and tremor of both hands. Prior to the administration of benzedrine she had been treated with atropine and scopolamine, with the usual results. At one time she was paroled, in the hope that she would be able to make a fair adjustment at home, since her husband was cooperative, but

two months later she had to return to the hospital. On Sept. 20, 1937 administration of benzedrine sulfate, 5 mg. twice a day, was started, and two months later the dose was increased to 10 mg. twice a day. No untoward effects of any significance were noted, although the patient had mild arteriosclerotic changes and her blood pressure was 140 systolic and 90 diastolic prior to the administration of benzedrine. After four months with this drug, her blood pressure was 120 systolic and 80 diastolic, and she was still apathetic and drowsy. Her weight remained unchanged. The patient did not notice any difference when a placebo was substituted for benzedrine; the nurses reported no change, nor did I find any noticeable variation.

Case 7.—C. C., a single man aged 27, had had acute encephalitis at the age of 15, followed by the gradual development of neurologic signs. However, he did not manifest psychotic symptoms until twelve years later, at the age of 27, when there developed marked emotional instability, fears, restlessness and transient episodes of excitement and agitation, during which he expressed suicidal and homicidal ideas. He had pill-rolling tremors, constant drooling of saliva, rigidity of the extremities and extremely advanced festination, which made walking difficult. He was admitted to the hospital in 1936 and was treated with stramonium, atropine and scopolamine. He always insisted that he felt best when he was receiving scopolamine. When he was treated with benzedrine sulfate he complained that his symptoms were more severe, and he did not become quiet until after two weeks, when he was again given scopolamine. During the time he was receiving benzedrine sulfate he was more active than before, and the mental picture presented was almost hypomanic. With placebo tablets resembling benzedrine the hyperactivity subsided, but subjectively he was not satisfied until the administration of scopolamine hydrobromide was resumed. He particularly liked the latter drug because his sleep disturbance was less troublesome while taking it. The blood pressure before treatment with benzedrine was 102 systolic and 68 diastolic and after two weeks with benzedrine was 127 systolic and 90 diastolic.

Case 8.—A. P., a man aged 24, was transferred in 1937 from a New York state hospital, where his condition was diagnosed as psychosis with epidemic encephalitis. The same diagnosis was made at the Hudson County Hospital. On admission he complained that his family mistreated him, because they would not always give him what he wanted. He was drowsy, irritable and at times argumentative and emotionally unstable and had outbursts of excitement. Neurologically he presented signs of parkinsonism; he had masklike rigidity of the face, festination with partial loss of automatic associated movements, rigidity of the extremities, tremor of both hands, monotonous speech and ophthalmoparesis. He had occasional oculogyric crises. He had been treated with stramonium for some time prior to admission to the hospital, and after admission was given atropine sulfate. On Sept. 20, 1937 treatment with benzedrine sulfate, 5 mg. twice a day, was started. During the first two weeks he seemed to improve slightly, became less drowsy and smiled when he replied to questions, although previously his facial expression had always been blank. The dose was increased to 10 mg. twice a day after the second week, but the improvement in the emotional sphere originally noticed did not progress. The oculogyric crises diminished in severity and frequency. He lost about 8 pounds (3.6 Kg.) during the four months he was receiving benzedrine sulfate. The blood pressure before treatment with benzedrine was 112 systolic and 80 diastolic; after treatment it was 128 systolic and 90 diastolic.

SUMMARY AND CONCLUSION

Because the group of patients with psychosis accompanying postencephalitis was small, the following conclusions are drawn with extreme reservations: 1. Benzedrine sulfate does not seem to produce any beneficial effects on the psychotic manifestations of postencephalitis.

2. When prolonged administration of the drug is desirable, it can be safely used provided the patients are properly selected, those with cardiac and vascular disease are excluded, individual idiosyncrasies are taken into consideration and the physician has an opportunity to keep the patient under close supervision.

3. It is doubtful if this drug presents any advantages, except for control of oculogyric crises, as compared with the drugs (atropine, scopolamine and stramonium) used in the past.

NOTE.—Since this paper was submitted for publication, 7 additional patients have been studied, making a total of 15. Essentially the same results were obtained.

PREPSYCHOTIC MEASUREMENTS OF PHYSICAL AND MENTAL GROWTH IN A CASE OF JUVENILE DEMENTIA PARALYTICA

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Data relative to yearly increments of physical and mental growth in childhood of patients with juvenile dementia paralytica obtained before antisyphilitic treatment are not found in the literature. At the time of hospitalization one usually finds the patient to be retarded physically and intellectually and can only infer from the history that this retardation has been existent over a period of years before the overt manifestation of a psychosis. On the other hand, measurements of growth obtained after the diagnosis of the condition are probably affected by the treatment instituted. An opportunity to collect early developmental measurements of a patient with a condition later diagnosed and treated as juvenile dementia paralytica was afforded me.

In 1922 the Harvard Graduate School of Education began a twelve year nonmedical study of 3,500 school children entering the first grade in three representative Massachusetts cities. Physical and mental measurements of these children were made each year as they progressed through the public school grades. In a survey of the admissions to the hospitals for mental disease of the state to discover patients in the group of 3,500 children who had become psychotic by their twentieth year, the following case of juvenile dementia paralytica was found.[1]

REPORT OF A CASE

Anamnesis.—A boy aged 15 years was admitted for the first time to the Boston Psychopathic Hospital on April 3, 1930. The history was given by a brother aged 29, who appeared to be reliable but was averse to saying much about the patient or his family. The principal complaint was progressive failure of mental abilities in a boy who previously had appeared to be normal, with the development of fears and temper tantrums.

Family History: The grandparents were unknown to the informant. The father, aged 55, a truckman, had had week-end bouts of alcoholic excess; he was emotionally unstable and subject to angry attacks, when the family did not do what he wanted; he had never struck any members of the family. The mother, aged 46, was calm and level headed. There was no history of venereal disease. There were four siblings: (1) A brother aged 29, married, was calm and healthy; his child and wife were also well. He had an attack of gonorrhea several years before, for which he was treated, with cure. (2) A sister died of cerebrospinal

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1. Dr. Walter F. Dearborn, of the Harvard Graduate School of Education, furnished the data on growth relative to this case, and Dr. C. Macfie Campbell permitted access to the patient's case history.

meningitis at the age of 7 or 8 months; she would have been 27. (3) A brother aged 21 was single; he was delicate and had frequent colds. (4) A brother aged 19 was normal. There were several miscarriages after the birth of the patient.

Developmental History: The patient's birth and early development seemed normal. He was breast fed. He walked at the age of 13½ months and talked at 15 months. Bowel and bladder control were acquired at the age of 24 months.

School History: The patient started in school at the age of 6 and did average schoolwork until he reached the fourth grade, at 10. Then there was a general falling off in his work, and he was not able to progress further, although he was placed in an "opportunity class." In the special class he did less and less work, finally becoming "uncooperative and stubborn."

Neurotic Traits: The patient exhibited nail biting, was irritable and cried easily. He had had a nightmare fourteen or fifteen months before, during which it was noticed that his face was lemon yellow. He was normal the next morning. He had temper tantrums, e. g., "if disturbed when sitting in a chair he would fly into a rage." This had been noticed during the past two or three years.

Personality: The patient had formerly been normal and had played with children of his own age. In the past two or three years he had become more childish and played with children of 7 or 8. He amused himself with tops and marbles. He was lethargic and slow in all movements. He wanted to be left alone. "If sent to a store he will laugh at the girl when she asks him what he wants." He could not adapt himself to the life of a child of his age. Mentally he was dull and apathetic.

Present Illness.—In the past year he had been frightened at many things, e. g., a shadow in the dark, traffic and automobiles; he had had many temper tantrums when disturbed in any way. The school record in the last three years had been very poor.

Mental Status.—The patient showed great resentment and fear on admission; he screamed and cried lustily and struggled violently whenever a hand was laid on him. His movements were a little slow. His facial expression was older than that of his years. In speech and acts he was like a child of 6 or 7 years. He used few words and had a lalling, baby type of speech, which showed inability to articulate properly. He resented keenly any attempt to touch him and cried lustily when held; he wandered aimlessly around, occasionally stamping his feet and showing a temper tantrum, pulled off his "Johnnie" and called for his coat, saying he wanted to go home.

Physical Findings.—The patient was rather poorly developed and showed a feminine type of pelvis and infantile genitals. There was no secondary hair on the body. The pupils were irregular and unequal and reacted sluggishly to light and in accommodation. The jaw deviated to the left. The right pupil was larger than the left and was sluggish to light. The patient was uncooperative and somewhat resistive during the examination. There were no bruises. The heart and lungs were normal. The abdomen was not relaxed. The deep reflexes were active.

Laboratory Findings.—The urine was cloudy and straw colored; specific gravity was 1.012; the reaction was acid; there was no bile, sugar, or albumin. Microscopic ammonium phosphate examination showed only crystals. The Wassermann reaction of the blood serum was positive.

Condition on Discharge.—The patient became quieter on the second day of his visit, but would not allow any one to approach or touch him. He was shy and apprehensive of the unfamiliar surroundings and expressed a fear of something

happening. After a ten day period of observation the patient was discharged from the hospital, and was to receive further antisyphilitic treatment in the outpatient clinic.

Diagnosis.—The clinical diagnosis was dementia paralytica.

Readmission.—The patient was admitted for the second time on July 15, 1930, at the age of 15 years and 3 months. Since the time of discharge he had become gradually worse. His behavior varied a great deal. On some days he was quiet, while on others it was impossible to do anything with him. Children in the neighborhood teased him, and he cried when they did so. He wanted everything he saw. The children on the street took things away from him. At home he ate a great deal, but not to the point of regurgitation; he did not seem to know when to stop. He was restless. He laughed and smiled at nothing. While at home he talked plainly, but for the last few weeks he had been mumbling. He mistook his aunt for his mother.

Mental Status.—General Behavior: On the day of admission the patient cried, struggled and wanted to go home all the time. On the day of examination he was much quieter. He was still overactive and restless and constantly wandered from one thing to another, seldom remaining quiet long. It was not possible to hold his attention long. He walked with a slow, waddling gait, and his posture showed marked stooping of the shoulders. There were no odd or unusual movements.

Summary.—The patient was very restless and undertalkative; speech was slurred and indistinct. There was marked wandering of attention. He was irritable, but fairly well oriented; his memory was defective. Physically, he was stout and undersized; the optic disks were pale; the pupils were of Argyll Robertson character; the jaw deviated to the left; the deep reflexes of the arms were hyperactive and unequal; the knee jerks were absent; the left plantar reflex was of extensor type; the posture was stooped, the gait waddling, and there were coarse tremors of the outstretched hands.

Laboratory Findings.—The Wassermann reaction of the spinal fluid was positive. The cerebrospinal fluid was cloudy and contained 4 small lymphocytes per cubic millimeter; the reaction for globulin was negative; the total protein was 60 mg., and the sugar 62 mg., per hundred cubic centimeters; the colloidal gold curve was 5543110000. The urine was straw colored and cloudy; the specific gravity was 1.010; the reaction was acid; bile, sugar and albumin were absent. Microscopic examination revealed only ammonium phosphate crystals. Examination of the blood showed 80 per cent (Tallqvist) hemoglobin and 11,800 white cells.

Condition on Discharge.—The patient showed no improvement mentally; serologically, however, there was slight improvement after antisyphilitic treatment. He was transferred to the Danvers State Hospital for institutionalization and continued treatment.

Data on Measurements.—The physical and mental measurements of this boy from 8 to 14 years of age, together with a graphic presentation of his retardation, are given in the accompanying table and in charts 1, 2 and 3.

Summary of Deviations.—Standing Height: At 8 years and 1 month the patient's height was 8 cm. less than mean. Nevertheless, it was well within the range of "normal." This comparative variation gradually increased through the years, the patient being 24 cm. below the mean height at the age of 14.

Gain: From 8 to 14 years of age the patient gained 5.8 cm. in height (expected gain, 31.27 cm.).

Data on Physical and Mental Measurements of an Italian Boy with Juvenile Dementia Paralytica

	Actual Measurements						Gain or Loss			
Age	8.1	9	11.1	12.1	13.1	14	9	12.1	13.1	14
Standing height, cm.	120.1	121.2	131.0	134.1	134.8	135.7	1.1	3.1	0.7	0.9
Sitting height, cm.	67.5	68.2	71.6	73.3	73.4	72.2	0.7	1.7	0.1	—1.2
Weight, Kg.	27.3	29.4	35.4	38.2	39.6	39.6	2.1	2.8	1.4	0.0
Head width, cm.	....	14.8	15.3	....	15.1	....	...	...	...	...
Head length, cm.	....	17.6	18.1	....	18.2	....	...	...	...	...
Leg length, cm.	52.6	53.0	59.4	60.8	61.4	63.5	0.4	1.4	0.6	2.1
Trunk length, cm.	44.7	44.2	46.1	47.4	47.2	46.7	—0.5	1.3	—0.2	—0.5
Iliac width, cm.	....	22.1	23.6	24.0	24.5	25.1	...	0.4	0.5	0.6
Chest depth, cm.	13.5	....	....	16.4	16.4	16.9	...	...	...	0.5
Chest width, cm.	18.5	....	....	20.7	21.2	21.2	...	...	0.5	...
Chronologic age	8.1	9.1	11.1	12.1	....	14				
Mental age	6.1	8.3	7.2	8.6	....	6				
Intelligence quotient	85	91	65	70	....	43				

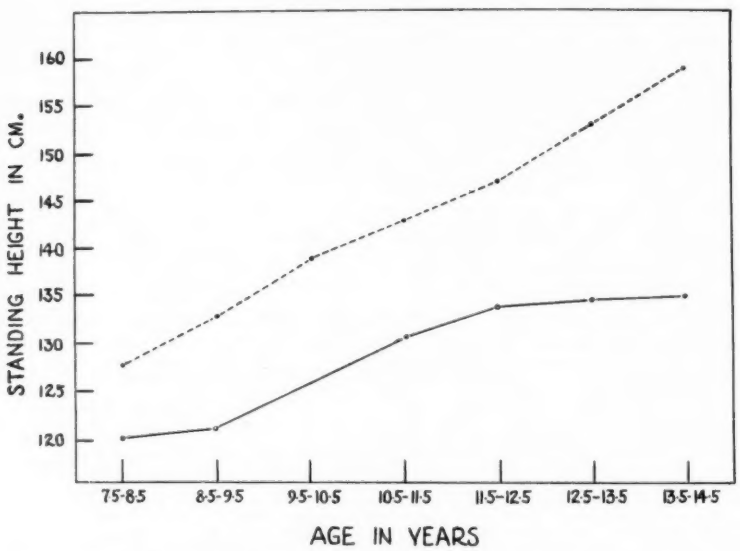

Chart 1.—Relation of standing height to age. In this chart and in chart 2, the normal mean is shown by a line of dashes, and the value for the patient with juvenile dementia paralytica, by a solid line.

Sitting Height: At 8 years and 1 month the sitting height was 1.7 cm. below the mean, this height, however, being within the normal range for this age. There was progressive emphasis of this variation, and at 14 years the patient was 10.1 cm. below the mean.

Gain: From 8 to 14 years of age the patient gained 2.5 cm. in sitting height (expected gain, 13.02 cm.).

Weight: At 8 years and 1 month the patient's weight was 1 Kg. above the mean, and it did not vary appreciably from the mean until the age of 13 and 14, when it was found to be 4 and 9 Kg., respectively, under the mean weight.

Width of Head: This was slightly above the mean at all examinations.

Length of Head: This was slightly under the mean at all examinations.

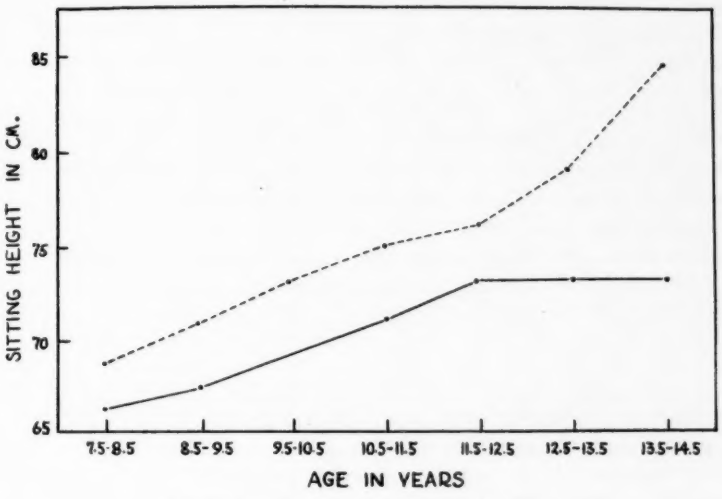

Chart 2.—Relation of sitting height to age.

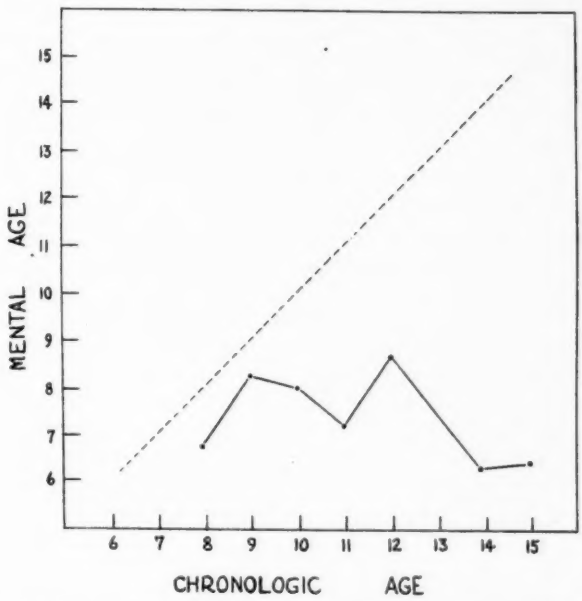

Chart 3.—Relation of mental to chronologic age. The normal value is shown by a line of dashes, and the value for the patient with juvenile dementia paralytica, by a solid line.

Depth of Chest: This was 2 cm. below the mean at 8 years and 1 month and 1.5 cm. below the mean at 14 years.

Width of Chest: This was 1.5 cm. below the mean at 8 years and 1 month and 4.7 cm. below the mean at 14 years.

Intelligence Quotient: At 8 years and 1 month the patient's intelligence quotient was 85; at 9 years and 1 month it was 91 (diagnostic group "of normal intelligence"). However, at 11 years and 1 month the intelligence quotient had dropped to 65; at 12 years and 1 month it was 70, and at 14 years, with the Stanford revision of the Binet scale, it was 43 (diagnostic group: "feebleminded").

Psychiatric Diagnosis (at the age of 15 years and 3 months).—The diagnosis was dementia paralytica.

Present Status.—The patient, now 23 years of age, was located in a state hospital for mental diseases, and a reexamination was made on Nov. 1, 1938. During the first of his eight years' hospitalization he was treated each week with an antisyphilitic regimen of arsenicals, mercurials and bismuth, but the general clinical condition improved only slightly and the Wassermann reactions of the blood and spinal fluid remained positive; In September 1934 the reactions were still positive, and a colloidal gold curve was 1111000000.

In November 1938 the patient's general physical condition was good. Both pupils were unequal and irregular and did not react to light. Physical measurements were: standing height, 152 cm.; sitting height, 83 cm.; weight, 55 Kg.; head width, 15.2 cm.; head length, 20 cm.; leg length, 76.2 cm.; iliac width, 25.2 cm.; chest width, 23 cm.; chest depth, 21 cm. It was impossible to gain the patient's cooperation or interest in an intelligence test.

The patient's daily behavior was described as follows: "An untidy, destructive, silly, distractible youth, who sometimes makes a brief reply to questions but more often does not. He knows this is a hospital and knows the attending nurse's name. His memory for early events is impaired. He has no hallucinations."

SUMMARY

The measurements of physical and mental growth of a child were obtained yearly over a period of six years prior to diagnosis, institutionalization and treatment in a case of juvenile dementia paralytica. The patient—essentially normal in development at the eighth and ninth year levels—showed definite retardation in physical growth and intellectual capacity at the age of 10 years, when he first failed seriously in school progress. During the next three years, prior to his hospitalization at 15, physical growth was virtually absent, and his learning capacity fell to the imbecile level. Antisyphilitic treatment since that time seems to have had a beneficial effect on the physical growth, but the mental retardation and behavior are unchanged.

ANEURYSM OF THE VERTEBRAL ARTERY

PETER BASSOE, M.D., CHICAGO

REPORT OF CASES

Two cases of aneurysm of the vertebral artery are reported for the following reasons: Large aneurysms of the vertebral arteries are rare. Subarachnoid hemorrhage may be the first manifest symptom. In spite of opinions to the contrary, syphilis is sometimes the cause. The clinical picture may lead to a suspicion of tumor of the brain.

CASE 1.—A married woman aged 31 was admitted to the Presbyterian Hospital on June 15, 1914, and twice later. The family history was unimportant except that the father died of tuberculosis. The patient was a timid, bashful, nervous child. Menstruation began at the age of 12 and ceased for a year at 14, during which she was weak and pale. She was married at the age of 17 and in the following year gave birth to a premature child, who had an eruption, "sore eyes and sore mouth" and died at the age of 3 months. She was told that the baby was syphilitic. Two years later she had a spontaneous miscarriage. As the husband proved to be a bigamist, she left him after five years. She married again at 25, had a miscarriage after a pregnancy of two months, then a baby who lived six weeks and died of erysipelas and finally, at the age of 29, a healthy child.

For six months before admission the patient had had headache, which was worse at night. Three weeks before admission the headache became severe; she was delirious for six hours and had two convulsions on the same day. A spinal puncture was made at that time; the husband was told that the fluid escaped at the rate of 175 drops per minute and that tests showed syphilitic meningitis. The headache continued, and there were attacks of unconsciousness, one on the day before admission.

Examination.—On admission the patient was drowsy, but answered questions correctly. She complained of pain over the vertex, occiput and back of the neck; on moving the head the pain extended to the sacrum. The skin was dry; the temperature was 99.4 F. The pupils were small but reacted to light and in accommodation. The neck was stiff; there was no definite Kernig sign. The knee and ankle reflexes were brisk. The heart, lungs and abdomen were normal. The leukocyte count was 21,500. Lumbar puncture yielded a uniformly bloody fluid, under increased pressure. The Wassermann reaction was negative with both the blood and the spinal fluid. Similar bloody fluid was obtained on June 18 and 19. No organisms were found in smears or cultures. There was a relative increase in lymphocytes. There was no papilledema, but the veins were rather prominent and the retinal cups a little obscured.

Course.—On June 18 the temperature rose to 102.6 F. and during the following eight days ranged from 99 to 100 F., in the morning, to about 102 F., in the evening. It was lower for a few days, and the patient felt better. On July 2 the spinal fluid was still bloody, with a count of 327 leukocytes, 81 per cent of which were

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Read at a meeting of the Chicago Neurological Society, Dec. 15, 1938.

mononuclears. The Wassermann reaction remained negative and the cultures sterile. The leukocyte count of the blood was 20,000 on June 17, 14,100 on June 21, 10,100 on June 26, 17,700 on July 5 and 16,600 on July 28. By July 10 the ankle, knee and abdominal reflexes were lost; the wrist and elbow reflexes were brisk. There was no Kernig sign, but the neck remained moderately stiff and tender. The right pupil was larger than the left. From July 4 to 13 the temperature reached 104 or 105 F. each evening; from July 14 to 20, 102 or 103 F.; on July 21, 105 F., and on July 22 and 23, 106 F. On July 17 the spinal fluid was of a uniform deep straw color, almost clear, and the pressure was only slightly increased; the cell count was 6; the Wassermann reaction was negative, and the Nonne-Apelt reaction was 2 plus. On July 29 the color of the spinal fluid was light straw, the cell count 4, the Wassermann reaction negative, the Nonne-Apelt reaction weakly positive and the colloidal gold curve 0222310000. After July 24 the temperature did not exceed 103 F.; after August 8 it was not higher than 101 F., and after August 14 it gradually declined to normal. On August 10 the left knee reflex was still brisk; the right knee and ankle reflexes were absent, however, and the left ankle reflex was very weak. On August 28 note was made of numbness in the right foot and leg and of paralysis of the tibialis anticus muscle and the extensor muscles of the toes. The knee and ankle reflexes were again present on both sides. The circumference of the right calf was 21 cm., and that of the left, 22 cm.

The general condition of the patient gradually improved, but the paralysis of the right foot remained and the atrophy increased. Sensation was normal. Reaction of degeneration was present. The patient was discharged in good general condition on November 20. In view of the history and in spite of the negative serologic reactions, inunctions of mercury were given daily during the first six weeks. During the following year the patient was seen occasionally, as the foot drop remained, but she was well otherwise.

Second Admission.—The patient was readmitted on June 3, 1916, complaining of occasional cramps in both legs, shooting pains in the left leg and occasional dizziness. The right pupil was still the larger. There was now only slight weakness in the right foot, but the atrophy remained. There was diminution of touch and pain sensation on the right side from the seventh thoracic level to the toes. The blood pressure was 120 systolic and 68 diastolic; the Wassermann reaction of the blood was negative. The spinal fluid was clear; the Wassermann reaction "weakly positive," the Nonne-Apelt reaction negative, the cell count 6 and the colloidal gold curve 1221100000.

Treatment was given for infection of the maxillary antrum and ethmoid cells on the right side. The patient was discharged on July 8, 1916. When seen again in April 1918 she felt well; the legs were strong, but there was still some atrophy in the right leg, and the right pupil was slightly larger than the left.

Third Admission.—The patient was readmitted on Sept. 2, 1937. She had been well until ten years previously, when the menopause began and she became nervous and often felt very weak, more so on the left side. She also complained of pain about the left ear, which radiated down the body, especially on the left side. Three months previously it had been discovered that she had high blood pressure, and since then she had vomited nearly every day.

On examination the blood pressure was 185 systolic and 100 diastolic. There was no definite local loss of motor power or sensation. The tendon reflexes were brisk and the plantar and abdominal reflexes normal. The pupils reacted normally,

and the eyegrounds were normal. Lumbar puncture yielded a clear fluid, with a cell count of 7, a negative Wassermann reaction, weakly positive reactions for globulin, a total protein content of 99.6 mg. and a sugar content of 64 mg. per hundred cubic centimeters. The colloidal gold curve was 0121111000. There was no fever on admission; on the second day, however, cough set in, the temperature and the leukocyte count rose, and physical signs of bronchopneumonia developed, together with cyanosis, difficulty in swallowing and absence of thoracic respiratory movements. The temperature reached 104 to 105 F. almost daily. The patient died on September 13.

Fig. 1.—Photograph of the aorta in case 1.

Autopsy.—The examination was made by Dr. Gurth Carpenter. The important items in the anatomic diagnosis were: saccular aneurysm in the region of the pons and bulb; syphilitic aortitis; atrophy of the cerebral cortex; unresolved bronchopneumonia; acute suppurative frontal sinusitis; emaciation; dehydration; generalized arteriosclerosis; atrophy of the right leg. The heart weighed 310 Gm. In the ascending portion of the aorta were three large, calcified plaques, one 15 by 9 mm. and the other 15 by 8 mm. In the abdominal aorta there were light, superficial fatty plaques (fig. 1). The anterior portion of the brain showed considerable cortical atrophy, wide sulci and an increased amount of subarachnoid fluid.

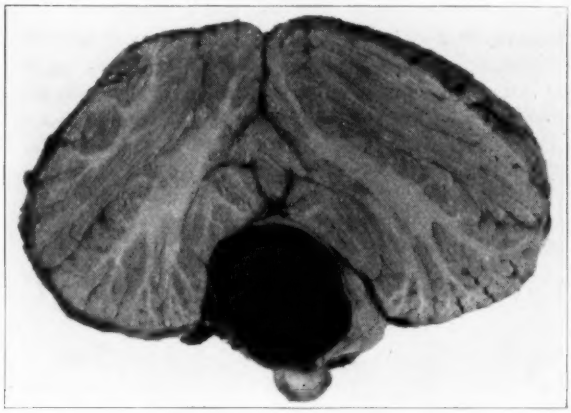

Fig. 2.—Aneurysm of the left vertebral artery in case 1.

Fig. 3.—Two basilar aneurysms on the ventral surface of the pons in case 1. A vertebral aneurysm appears on the left side of the bulb.

After hardening in formaldehyde, the brain was sectioned. There was only moderate thickening of the leptomeninges over the vertex, and the edematous appearance of the fresh specimen was largely lost. The bulb was greatly displaced to the right by a firm, dark red mass, 3.5 by 3 cm. This was found to be an unruptured aneurysm of the left vertebral artery (fig. 2), having an indurated wall and containing a firm, dark red, adherent clot. In the basilar artery, less than 1 mm. beyond the union of the two vertebral arteries, was a globular aneurysmal dilatation, 12 mm. wide. Within 5 mm. of the upper bifurcation of the basilar artery was a third, more yellow, aneurysm, 1 cm. long and 4 mm. wide (fig. 3). A fourth, rust-colored, circular nodule, 5 mm. wide, was observed inside the bulb, 3 mm. from the pial surface and 1 cm. from the floor of the fourth ventricle. All these aneurysms were unruptured, had thick walls and contained old clots, but the subarachnoid hemorrhage occurring in 1914 undoubtedly had been caused by rupture, later healed, of a similar aneurysm.

Histologic Examination.—The diagnosis of syphilitic aortitis was supported by the observation of small scars in the outer part of the media, away from the atheromatous patches. Subintimal proliferation in small vessels in the aneurysmal walls was also seen. Otherwise, all vessels showed marked nonsyphilitic arteriosclerosis. Prolonged search for spirochetes in the aorta and walls of the aneurysms gave negative results. Here and there round cell infiltrations were seen in the meninges of the cord. Degeneration of both pyramidal tracts was moderate in the cervical and thoracic regions and slight in the lumbar region.

CASE 2.— A man aged 52 was seen at his country home on June 26, 1921, in consultation with Dr. G. A. Carhart, of Milwaukee. The family history presented nothing of interest. The patient had been well in childhood. At the age of 14 years he received an injury to the left eye, resulting in loss of vision. Eighteen years before examination he had been treated for an illness associated with enlargement of the liver. At one time he had an attack in which he lost himself in the street; he was confused for a few hours and remained in bed for a week. After that he had considerable headache, especially during the last five years. He stopped smoking, but continued to chew tobacco. Five years before examination he had several attacks of dizziness and severe headache, usually at night, without vomiting. Dizzy spells occurred occasionally after this. Three years ago he went to Washington, D. C., and worked much harder than before. One night, while there, he complained of numbness of one side of the body, which persisted, and there was also dragging of one foot. Five days before my seeing him, after fishing on a hot day, he had a severe attack of vertigo while in the boathouse, which seemed to him to have turned upside down. While there, he may have had a convulsive seizure. The next day his speech was thick; he could not walk alone and had frequent clonic spasms of the right arm and leg and difficulty in swallowing. The following day there were also spasms of the right arm. On June 24, in the morning, he had a generalized convulsion, not severe, during which he was unconscious and had involuntary micturition. There was no spasm after that, and speech improved.

Examination.—There were a Babinski sign bilaterally and slight ankle clonus. Both knee jerks were increased, the left more than the right. The cremasteric reflexes were normal and the abdominal reflexes absent. The wrist jerks were present, the left being greater than the right. The elbow jerks were normal. Pain and temperature sensation were impaired on the left side of the body, except over the face. There was slight ataxia of the right hand. There was a subjective

sensation of burning over the right side of the face. The patient was able to walk with a little aid. The right leg was slightly weak, the speech a little thick.

Lumbar puncture yielded a clear fluid; the cell count was 7; the Wassermann reaction was negative; the Nonne-Apelt reaction weakly positive; the colloidal gold curve was 0122221100. A few days before, a negative Wassermann reaction of the blood had been obtained; the blood pressure was 120 systolic; the urine was normal.

Diagnosis.—I made a tentative diagnosis of a vascular lesion in the pons and bulb.

Course.—The patient improved for a few weeks and then went to the Johns Hopkins Hospital for further study. Dr. Walter Dandy wrote me on Aug. 30, 1921: "The patient was in a deplorable condition when he came here. He was scarcely able to walk. His remaining eye was turned far to the outside." Suspecting a tumor in the brain stem, Dr. Dandy explored the posterior fossa and found "a vascular aneurysm with a tremendous enlargement of the left vertebral artery." The wound was closed, and it was planned to ligate the vessels and remove the aneurysm later. However, a few days after the exploration, the patient had more convulsions and died.

COMMENT

The causes of intracranial aneurysms are generally given as congenital defect in the vascular walls, arteriosclerosis, trauma, septic embolism and syphilis. There is some difference of opinion as to the frequency of syphilis as a cause of this condition, some authors virtually ignoring it. Considerable search of the literature has led me to believe that syphilis rarely produces the rather common small aneurysms on the circle of Willis, while it is less rare as a cause of the more infrequent large aneurysms of the basilar and vertebral arteries. In a recent article, entitled "Syphilis as the Most Frequent Cause of Aneurysm at the base of the Brain," Maass,[1] a German pathologist, found histologic evidence (in some cases rather meager!) of syphilis in all of 4 cases of aneurysm of these vessels. There have been several reports of such aneurysms in syphilitic subjects, without evidence of syphilitic disease of the arteries concerned. Beadles [2] collected 555 cases of fatal cerebral aneurysm, in 3 of which a vertebral artery was involved. Von Hoffmann [3] saw 78 cases personally; in 10 the aneurysm affected a vertebral artery, the left in 7, and in 10, the basilar artery. All the aneurysms had ruptured. Among cases in which the aneurysm was ascribed to syphilis were 1, described by Boinet,[4] in which an aneurysm of the left vertebral artery, 30 by 15 mm., was associated with gummas of the brain and meninges and 1, described by Hedinger,[5] of a syphilitic patient who had been hemiplegic for eight years, in which an aneurysm the size of a hazelnut, involved the right vertebral artery.

Death occurs most frequently from rupture, causing profuse subarachnoid hemorrhage. In all cases of such hemorrhage aneurysm should be thought of, and repeated hemorrhages together with focal

1. Maass, U.: Beitr. z. path. Anat. u. z. allg. Path. **98**:307, 1937.
2. Beadles, C. F.: Brain **30**:285, 1907.
3. von Hoffmann, E.: Wien. klin. Wchnschr. **7**:824, 1894.
4. Boinet, E.: Compt. rend. Soc. de biol. **69**:210, 1910.
5. Hedinger, E.: Cor.-Bl. f. schweiz. Aerzte **35**:26, 1905.

symptoms may lead to a correct diagnosis during life. Focal symptoms were pronounced in a case of aneurysm of the left vertebral artery described by von Monakow and Ladame:[6]

There were violent attacks of vertigo with unilateral deafness and tinnitus, ataxia, dysphagia, dysarthria, irregular pulse and heterolateral anesthesia. Death occurred from respiratory failure.

A large aneurysm of the left vertebral artery was shown at a meeting of the Chicago Neurological Society by Dr. H. G. Wells.[7] It was taken from a Negro aged 54 who had complained of weakness, dizziness, tinnitus and pain in the left side of the face. Dandy,[8] on opening the head for the purpose of cutting the vestibular nerve in a case of Ménière's syndrome, with tinnitus in the left ear, variable deafness and diminished left corneal reflex, observed an aneurysm of the left vertebral artery. I found only 1 case in which a bruit was described; it was heard between the mastoid process and the spine in a case of aneurysm of the left vertebral artery, reported by Moser,[9] in which there had been "prolonged bulbar symptoms."

DISCUSSION

Dr. Carl W. Apfelbach: Gross and histologic evidence of previous syphilitic inflammation was seen in the aorta. In the descending portion of the arch and the superior half of the thoracic portion of the aorta there were fatty, fibrous and calcified plaques, whereas the abdominal portion was not altered significantly by sclerosis. Microscopic preparations from the root and thoracic portion of the aorta revealed scars in the outer third of the media that had replaced the elastic and muscle fibers. No active evidence of inflammation was observed.

In the walls of the cerebral aneurysms there was chiefly hyalinized scar tissue. Because of this, there was little to interpret in so far as syphilitic arteritis is concerned. In contrast to the extensive changes in the walls of the aneurysms, the remaining portions of the cerebral arteries were free from sclerosis.

The anatomic observations allow the diagnosis of a previous syphilitic inflammation of the aorta and exclude arteriosclerosis as a factor in production of the aneurysms. Moreover, the alterations in the wall of the aneurysms were consistent with the changes usually observed in the wall of a saccular aneurysm resulting from syphilitic arteritis.

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6. von Monakow, C., and Ladame, P.: Nouv. iconog. de la Salpêtrière **13**:1, 1900.

7. Wells, H. G.: Intracranial Aneurysm of the Vertebral Artery, Arch. Neurol. & Psychiat. **7**:311 (March) 1922.

8. Dandy, W. E.: Pathologic Changes in Ménière's Disease, J. A. M. A **108**:931 (March 20) 1937.

9. Moser, H.: Deutsches Arch. f. klin. Med. **35**:418, 1884.

Obituaries

DONALD GREGG, M.D.
1881-1939

Dr. Donald Gregg died at the Massachusetts General Hospital on Jan. 6, 1939, of malignant disease of the esophagus. At the time of death he was 58 years of age and seemingly at the height of his intellectual power.

Dr. Gregg was born in Hartford, Conn., but received his schooling in Colorado Springs, Colo., where his father was a minister. Thence he went to Harvard College, graduating in 1902. Then followed a year of teaching in Milton Academy, followed by four years at the Harvard Medical School, from which he graduated in 1907. After internship at the Massachusetts General Hospital, Gregg continued his medical training in Manila, P.I., for about two years. He thus obtained a broader foundation in medicine than was at that time considered necessary for a psychiatric career.

For a brief period Gregg was associated with Dr. Elmer E. Southard in the then new Boston Psychopathic Hospital, but in 1912 he joined Dr. Walter Channing and moved with him in 1916 to new quarters in Wellesley, Mass. In 1922, at Dr. Channing's death, Gregg took full charge of the Channing Sanitarium, a post he held until his death.

To psychiatry Gregg brought a well trained medical mind, a point one was never allowed to forget, for he deemed it essential in an approach to psychiatry. For this reason he was neither led nor misled by fashions, either in medicine or psychology. This does not imply that he was not progressive in thought and deed, as indicated by his constant attendance at meetings, in which he was frequently an active participant. His interests were broad, and he could hold his own in constructive conversation, whether in the field of medicine, religion, politics or literature. Son of a minister, with six brothers and sisters in various professions, it was natural that he should have wide interests.

During the last decade, Dr. Gregg, as president of the Massachusetts Society for Mental Hygiene, found the outlet necessary for one with ambition beyond the boundary of his own institution and entered heartily into the growing work of that society. It is perhaps a pity that Dr. Gregg's life and work in Wellesley made it impossible for him to enter the academic field, for his well balanced mind, keen interest in the new and general fairness would have made him a valuable teacher, as he was a successful practitioner.

His keen sense of humor enabled him to make happy adjustments to the problems in his own personal life. Blessed with an optimistic and stable temperament and possessing a practical philosophy of life, he gave his patients that comfort and reassurance they sought.

JAMES B. AYER, M.D.

Abstracts from Current Literature

Anatomy and Embryology

INNERVATION OF THE HYPOPHYSIS. A. T. RASMUSSEN, Endocrinology **23**:263 (Sept.) 1938.

This study is based on an investigation of the hypophyses of 47 adults and 1 newborn infant. The glands were cut serially in various planes and stained by the Cajal and Golgi methods. Thirty-two of the hypophyses were prepared by a modification of the pyridine-silver method. Five well impregnated hypophysial stalks were examined in a study of the fibers in the tractus hypothalamicohypophyseus and of cells in the nucleus supraopticus. The number of fibers in the hypophysial tract from the hypothalamus varied from 40,000, in the newborn, to 69,000, in adults. The complexity formed by these thousands of nerve fibers in the processus infundibuli is difficult to describe. This relatively enormous nerve supply appears to be out of proportion to the cellular content of the neural lobe and to the amount of epithelium in the pars tuberalis, pars infundibularis and pars intermedia. One is almost forced to assume that the hormones produced by the neural lobe are liberated without the intervention of secretory cells in the usual sense, as in the humoral mechanism associated with the sympathetic nervous system. There are at least 50,000 fine unmyelinated nerve fibers descending from the hypothalamus into the infundibulum, and there are as many cells in one supraoptic nucleus.

Large areas of the pars intermedia may be devoid of nerve fibers, whereas other parts, especially those associated with the basophilic cells, are rich in nerve fibers. Many of the nerve fibers encountered in the pars intermedia appear to be only incidental. A number of structures suggest nerve terminals on the cells of this region. Many of these are apparent rather than real, but a few cannot be thus disregarded. In the connective tissue capsule of the hypophysis there are numerous small unmyelinated nerves. They are most conspicuous on the upper surface of the anterior lobe. They are derived from the cavernous sympathetic plexus and probably represent about 200 fibers. A few of these ascend along the blood vessels of the stalk. A conspicuous number pass into and along the vascular stroma anteriorly and laterally in the upper superficial part of the anterior lobe. A few individual fibers ultimately ramify among the epithelial cells. A large right and a left group of fibers, commencing just lateral to the stalk, descend deeply into the corresponding half of the anterior lobe, where they usually become associated with prominent blood vessels. Some of these fibers are disseminated among the gland cells of a limited region deep in the anterior lobe. Several small capsular nerves pass downward and forward, sending a few fibers into the substance of the anterior lobe at numerous points. The larger strands are usually near arteries or veins. Individual fibers from this source intertwine among the gland cells, but they rarely penetrate far into the lobe. No definite nerve terminals are seen strictly in the anterior lobe. Some of the capsular fibers have been followed along blood vessels into the neural lobe, where they become lost in the dense nerve plexus. Such a large proportion of the anterior lobe appears to be so devoid of nerve fibers that the presence of secretory nerves to this part of the hypophysis remains highly questionable. The nerve fibers in this lobe are probably connected with the vascular system.

PALMER, Philadelphia.

THE NEURONE AS STUDIED BY MICRO-INCINERATION. L. ALEXANDER, Brain **61**: 52, 1938.

Using the microincineration method for the study of nerve cells, Alexander arrived at the fololwing conclusions: 1. Ganglion cells contain rich deposits of heat resistant mineral ashes in the nucleolus and in the Nissl bodies of the cyto-

plasm and dendrites. 2. The intracellular neurofibrils, the axon hillock and the main body of the axis-cylinder are free from heat-resistant mineral ashes. 3. The lipoid part of the myelin sheath is free from mineral ash. 4. The myeloaxostroma contains a small amount of heat-resistant mineral ash. 5. The granular cells of the cerebellar cortex and the ganglion cells from allocortical areas are richer in mineral ash residue than morphologically similar ganglion cells from isocortical areas or from the basal ganglia. In addition, there is a great deal of variation in the mineral distribution, corresponding to cortical architectural fields. 6. The content of heat-resistant mineral ash in the same neuron is relatively greater during ontogenetic development than after differentiation. 7. The fact that the content in heat-resistant mineral ash is greater in ganglion cells than in nerve fibers, and relatively greater in ganglion cells during ontogenetic development than after differentiation, suggests a positive correlation of the heat-resistant mineral ash with growth and metabolic activity. SALL, Philadelphia.

THE RUBROSPINAL SYSTEM IN MONKEY AND MAN. W. J. C. VERHAART, Psychiat. en neurol. bl. **42**:335, 1938.

The central tegmental tract originating in the frontal part of the red nucleus is not constant in monkeys and is very small when present, while the rubrospinal tract is always demonstrable. The opposite is true in man. In a patient with an old softening of the tegmentum and pons and in another with a pontile lesion only no degeneration was visible in the rubrospinal tract. In the case of a lesion destroying the internal capsule and the lenticular and lateral thalamic nuclei, as well as the triangular field in the medulla oblongata, a small area of degeneration was observed in the region of the rubrospinal bundle. The red nucleus changes its character during its phylogenetic development from a purely motor nucleus to one more intimately connected with the olivocerebellar system. It is not permissible to compare all kinds of increased tonus with decerebrate rigidity. The latter exists with and without interruption of the rubrospinal tracts. In man the hemispheres exercise a great influence on muscular tonus. LEWY, Philadelphia.

COMPARISON OF THE CORPUS STRIATUM AND THE RED NUCLEUS AS SUBCORTICAL CENTERS OF THE CEREBRAL MOTOR SYSTEM. W. J. C. VERHAART, Psychiat. en neurol. bl. **42**:676, 1938.

The basal ganglia neither receive an appreciable number of afferent fibers from the cortex, thalamus or mesencephalon nor depend in their development on the thalamocortical complex or the red nucleus. Very thin fibers originating in the putamen and caudate nucleus end partly in the globus pallidus and partly in the corpus subthalamicum, mesencephalon and pons. There are no fibers connecting the putamen and the caudate nucleus. The thick pallidal fibers run to the nuclei in the wall of the third ventricle, to the corpus subthalamicum and to the laterofrontal nuclei of the substantia nigra. Fine fibers from the caudate nucleus and putamen pass the red nucleus to end in the reticular nuclei of the mesencephalon and pons. In lower mammals the red nucleus is an important motor reflex center. A part of the long ascending tracts end here, while the rubrospinal tract proceeds directly to the nuclei of the cranial nerves and the spinal cord. In higher mammals the thalamocortical system takes over a large part of the function of the red nucleus. In the course of this development the motor portion of the red nucleus and its descending rubrospinal tract become smaller, while the anterior portion of the nucleus increases in size. This portion is part of the cerebellorubroolivary system. It plays an important role in crossed cerebrocerebellar atrophy.

LEWY, Philadelphia.

Physiology and Biochemistry

DEGENERATION OF INFUNDIBULAR NERVE FIBERS IN THE CAT WITHOUT APPRECIABLE POLYDIPSIA. ALLEN D. KELLER and J. WILLIAM HAMILTON JR., Arch. Surg. **37**:760 (Nov.) 1938.

The hypophysis was isolated from its entire direct hypothalamic nerve supply in several cats without the production of appreciable polydipsia.

GRANT, Philadelphia.

CHANGES IN LIPID COMPOSITION OF NERVES FROM ARTERIOSCLEROTIC AND DIABETIC SUBJECTS. LOWELL O. RANDALL, J. Biol. Chem. **125**:723, 1938.

The phosphatide, cholesterol, cerebroside, neutral fat and water contents of the femoral, sciatic and posterior tibial nerves of normal, diabetic and arteriosclerotic subjects were determined. The femoral, sciatic and posterior tibial nerves from normal subjects did not show significant differences in composition. The peripheral nerves from diabetic and arteriosclerotic subjects showed marked decrease in phosphatide, cholesterol and cerebroside constituents and an increase in neutral fat, but no significant change in water content. The posterior tibial nerve showed more extensive changes from normal than the sciatic, and the sciatic nerve more than the femoral. The similarity of the extent and quality of the chemical change in the two disease processes indicates a common factor operating in them. The greater extent of chemical change in the more distal parts of the nerves indicates that an inadequate blood supply and the concomitant anoxemia are the immediate causes of the decomposition of the lipid constituents, the structural elements of the nerve fibers.

PAGE, Indianapolis.

THE OXYGEN UPTAKE OF TISSUES IN VITAMIN DEFICIENCIES. BARNETT SURE and J. B. DEWITT, J. Biol. Chem. **126**:287, 1938.

Measurements of the oxygen uptake of several tissues of albino rats were made by Sure and DeWitt with the Barcroft apparatus. The experiments were carried out by the paired feeding method, the daily food intake of the animals serving as controls having been restricted to the same plane of nutrition as that of the pathologic litter mates during the previous twenty-four hours. The results, expressed as the percentage of reduction in oxygen uptake, are summarized as follows: Deficiency of vitamin B complex: kidney (21 groups), 15 per cent; heart (9 groups), 18 per cent. Vitamin B_1 deficiency associated with polyneuritis: cerebrum (16 groups), 16 per cent; heart (14 groups), 17 per cent; kidney (19 groups), 19 per cent. Vitamin A deficiency: cerebrum (13 groups), 14 per cent; heart (7 groups), 19 per cent. The quantitative reduction in oxygen uptake of the kidney, heart or cerebrum of albino rats given diets deficient in vitamin B complex, vitamin B_1 or vitamin A was not influenced by the extent of loss of weight, severity of polyneuritis or severity of ophthalmia, respectively.

PAGE, Indianapolis.

METABOLIC INVESTIGATIONS ON A CASE OF PHENYLPYRUVIC OLIGOPHRENIA. GEORGE A. JERVIS, J. Biol. Chem. **126**:305, 1938.

Fölling found phenylpyruvic acid in the urine of 10 mentally defective patients. The term phenylpyruvic oligophrenia has been proposed for this condition. Jervis studied the effect of feeding the following pure amino acids on the urinary output of phenylpyruvic acid: phenylalanine, tyrosine, tryptophan, phenylserine, dihydroxyphenylalanine, alanine, leucine, cystine, valine and aminoacetic acid. Of these, only phenylalanine increases the urinary output of phenylpyruvic acid. The dextro form of phenylalanine induces a greater increase in phenylpyruvic acid than the levo form. Formyl- and acetyl-d-phenylalanine do not yield phenylpyruvic acid, whereas the corresponding derivatives of l-phenylalanine increase the excretion of

phenylpyruvic acid. The ingestion of phenylpyruvic and phenyl-lactic acids leads to increased excretion of phenylpyruvic acid. Phenylpropionic, phenylglyceric, cinnamic, p-hydroxyphenylpyruvic and homogentisic acids fail to augment the output of phenylpyruvic acid. Jervis concludes that the disease is characterized biochemically by inhibition of the metabolism of phenylalanine at the stage of phenylpyruvic acid, the subject being unable to oxidize this ketoacid at a normal rate.

PAGE, Indianapolis.

RADIOACTIVE PHOSPHORUS AS AN INDICATOR OF PHOSPHOLIPID METABOLISM: IV. THE PHOSPHOLIPID METABOLISM OF THE BRAIN. G. W. CHANGUS, I. L. CHAIKOFF and S. RUBEN, J. Biol. Chem. **126**:493, 1938.

The phosphatide metabolism of the rat brain was investigated with radioactive phosphorus as indicator. After ingestion of labeled phosphate, the brain shows a much slower deposition of radioactive phosphatide than the liver, kidney or small intestine. A progressive increase was observed as long as two hundred hours after administration of the phosphorus. Once the maximum amount of labeled phosphatide has been deposited, its loss from the brain occurs at a very slow rate. Radioactive phosphatide was found as late as four weeks after the labeled phosphorus was fed. The rate of formation of brain phosphatide is identical in fed and in fasting rats. The brain of young rats incorporates radioactive phosphatide in greater amounts than that of adults.

PAGE, Indianapolis.

HETEROPLASTIC TRANSPLANTATION OF SOMITES. S. R. DETWILER, J. Exper. Zoöl. **79**:361 (Nov.) 1938.

The sixth, seventh and eighth somites of Amblystoma punctatum embryos were replaced on one side by corresponding somites from Amblystoma tigrinum embryos. The volume of muscle on the side of the tigrinum transplants increased from 20 to 70 per cent over that on the normal side, the differences being greater in older than in younger larvae. The adjacent spinal ganglia on the tigrinum side, however, did not undergo any hyperplastic response. Proliferative responses of ganglion cells to muscle changes were related primarily to alterations in the number of muscle fibers rather than to mass. The increased volume of muscle on the tigrinum side was due principally to an increase in size rather than in number of fibers. The ganglia, therefore, did not hypertrophy. The vertebral arches, of sclerotomic origin, became enormous on the tigrinum side as compared with those on the punctatum side. The corium of the skin on the two sides was similar in thickness and structure, but the epidermis was thickened on the tigrinum side. Replacement of the brachial somites of Amblystoma punctatum by a strip of unsegmented axial mesoderm from tigrinum embryos led to the formation of several supernumerary somites on the tigrinum side, with a corresponding numerical increase in the spinal ganglia and peripheral nerves. The conclusion that the typical segmentation of peripheral spinal nerves is subservient to the segmentation of the mesoderm is thus supported.

WYMAN, Boston.

THE GUSTATORY NATURE OF THE CHEMOTARSAL STIMULATIONS IN THE HOUSEFLY, MUSCA DOMESTICA L. C. C. DEONIER, J. Exper. Zoöl. **79**:489 (Nov.) 1938.

Unfed adult houseflies, about 20 hours old, were used. The chemoreceptors of the tarsi or the oral lobes were stimulated with a one molar solution of sucrose, using modifications of the brush-needle method or the screen wire and watch glass method of McIndoo. An extension of the proboscis was taken as a positive response. The flies did not give an olfactory response to the sucrose solution, but responded only when it came in contact with the tarsi or the oral lobes. It is evident, therefore, that the so-called olfactory pores on the tarsi must be capable of receiving taste stimuli such as solutions of sucrose give, or that other sense organs, as yet undescribed, must exist which are capable of receiving taste stimuli.

WYMAN. Boston.

STUDIES IN EQUILIBRIUM REACTION. STEPHAN WEISZ, J. Nerv. & Ment. Dis. **88**:150 (Aug.) 1938.

Proprioceptive body reactions serve to integrate the distribution of muscle tone within the body; the equilibrium reactions adapt the position of the body to changes in the supporting surface. Weisz studied the equilibrium reactions in 67 children, varying in age from 2 months to 11 years, with special attention to the time of their appearance and the course of their development. In his investigations he altered the supporting surface by tipping the examining table on which the subject had been placed in the sitting, standing, prone, supine or quadruped position. The responses were analyzed into two components: (1) compensatory movements which bring the extremities into a new position proper for equilibrium, and (2) a change in "support tonus." Rademaker has shown that the equilibrium reactions are produced by labyrinthine excitation and are lacking only when there are disturbances in the labyrinth or in the central labyrinthine tracts. The normal responses in the prone or supine position consist of increase of the support tonus by stretching out the extremities to the side on which the (upward) tipping occurred, with compensatory movement of the hip and shoulder and abduction of the corresponding extremities. The head and trunk may turn opposite the direction of the tipping, so that the body forms an arc with the concavity upward. In the sitting and standing positions the compensatory movements consist of rotation of the trunk and displacement of the extremities opposite the direction of tipping, while support tonus is increased by stretching out on the side of the tipping. Similarly, characteristic reactions are observed when the subject is in the quadruped position. The "see-saw" reaction is tested with the subject in the standing position, by raising one leg passively and pushing the trunk toward the side of the lifted leg, whereon a strong extension and abduction of the lifted leg occurs.

According to Weisz, these reactions occur first at the age of about 6 months. Analyses of the reactions in normally developing children of various ages established a clear relation between the learning of sitting, standing and walking and the equilibrium reactions appropriate to each. Children who were retarded in the acquirement of sitting, standing and walking were correspondingly late in exhibiting the equilibrium reactions. Thus, the equilibrium reactions were lacking in the first period of life and appeared in the course of development and paralleled it. While the body righting reactions gradually disappeared in the course of the child's development, the equilibrium reactions increased in strength and importance. In cerebellar disturbances the equilibrium reactions not only were present but were executed briskly and hypermetrically. The disturbances resulting from cerebellar lesions consisted, therefore, not in inability to maintain equilibrium but in inability to regulate and control the required movements. Hence, the functions of the cerebellum should be considered as inhibitory to the primitive equilibrium reactions.

MACKAY, Chicago.

MECHANISM OF CARDIAZOL [METRAZOL] CONVULSION. J. A. F. DENYSSEN and D. J. WATTERSON, J. Ment. Sc. **84**:1002 (Nov.) 1938.

From their experimental results with 32 patients undergoing or about to undergo metrazol convulsions, it appears to Denyssen and Watterson that the effects of metrazol on the circulation occur solely through the vasomotor center. The chief of these effects is vasoconstriction. Experiments with amyl nitrite and histamine demonstrate that vasodilatation antagonizes the action of metrazol, as under appropriate conditions it prevents the convulsion from occurring. The conclusion is that the convulsion itself is due to a vascular spasm. J. A. M. A.

VARIATIONS IN THE BLOOD SUGAR PRODUCED BY INJECTION OF METRAZOL IN PATIENTS WITH SCHIZOPHRENIA. P. CLÉMENS, J. belge de neurol. et de psychiat. **38**:357 (May) 1938.

Clémens observed the blood sugar level during the course of metrazol treatment of schizophrenic patients and demonstrated that metrazol when injected in a sufficiently large dose produces hyperglycemia. There was an appreciable rise

in blood sugar within fifteen seconds after the drug was administered intravenously, and after fifteen minutes when it was administered intramuscularly. When an epileptiform attack was produced by the injection, the hyperglycemia generally appeared before the onset of the attack. The tonic and clonic phases of the attack occurred simultaneously with a decline in the blood sugar, but the author observed no hypoglycemia during the paroxysms. Consequently, he believes that there is no relation between the modifications in the blood sugar following the injection of metrazol and those associated with the use of insulin. The hyperglycemia which follows the injection of metrazol is not related to the production of the epileptiform attack and can be obtained in cases in which no such attack occurs. Clémens believes that a rise in blood sugar following the injection of metrazol is the result of stimulation of the sympathetic nervous system.

DE JONG, Ann Arbor, Mich.

ROLE OF VITAMIN B_1 IN HUMORAL REGULATION OF THE NERVOUS SYSTEM. B. MINZ, Presse méd. **46**:1406 (Sept. 21) 1938.

Minz reviews Loewi's theory of the humoral transmission of the nerve impulse which assumes the liberation of two antagonistic substances at the nerve terminations, one of the type of acetylcholine and the other of the type of epinephrine. After citing recent investigations on the role of acetylcholine in the excitation of the nerves, he reports some of his own observations which suggested to him that the extract of the nerve that had been subjected to excitation contained, in addition to the substance of the acetylcholine type, a second substance which reenforced the action of the first. Investigations on the nature of this substance disclosed that its action was that of a ferment. Consequently, he searched for a substance with this type of action in yeast, and experience confirmed the supposition that this substance exists in yeast. In view of the fact that yeast is rich in vitamins, particularly the vitamins the deficiency of which produces nervous disturbances, he investigated whether the substance might be identical with the antineuritic factor, that is, vitamin B_1. He showed that vitamin B_1 is capable of strengthening the effect of acetylcholine and that in the humoral mechanism of nervous excitation vitamin B_1 assumes a role of coferment of acetylcholine. The absence of the coferment of acetylcholine explains some symptoms of beriberi, such as tachycardia, the disappearance of the patellar and achilles tendon reflexes, the disturbances of coordination, the atrophy of the muscles and the neuritic, paralytic and gastrointestinal disorders. Moreover, it is known that several of these phenomena are present in febrile diseases, such as malaria, typhoid, dysentery and pneumonia, and even in the banal infections. Finally, they are observed in the course of conditions which are accompanied by augmentation of metabolism (pregnancy, lactation and physical exertion). These symptoms are brought on by the factors which increase the organism's need for vitamin B_1. Among the agents which disrupt the optimal equilibrium between acetylcholine and vitamin B_1 there is, in addition to certain micro-organisms, the cancerous cell, a fact which is of great importance for the study of cancer. Favorable therapeutic effects of vitamin B_1 have been observed in cases of neuritis and even in several cases of multiple sclerosis, as well as in treatment of the nervous symptoms of pernicious anemia. In discussing the last disease, the author points out that favorable therapeutic results have been obtained with acetylcholine. However, because the action of this substance is of extremely short duration, he thinks that the preliminary administration of vitamin B_1 will make the action of acetylcholine more intensive and lasting.

EDITOR'S ABSTRACT.

THE HUMAN ELECTROENCEPHALOGRAM. H. BERGER, Arch. f. Psychiat. **108**:407 (June) 1938.

Berger found that in epilepsy, after the convulsion and while the patient is unconscious, there is an absence of alpha waves, and the beta waves control the

picture. A similar type of record can be obtained during an "absence." He agrees with investigators who maintain that these changes cannot be due merely to disturbances of action currents of the muscles. MALAMUD, Iowa City.

FLUCTUATIONS IN CHOLESTEROL CONTENT IN CASES OF MULTIPLE SCLEROSIS. E. PICHLER and H. REISNER, Wien. klin. Wchnschr. **51**:1304 (Dec. 9) 1938.

Pichler and Reisner, who for different reasons made studies on the serum cholesterol content of patients with multiple sclerosis, found that the cholesterol values are not constant, but undergo fluctuations. Since many aspects of cholesterol metabolism are still obscure, they studied the cholesterol content of the serum in a large number of cases of multiple sclerosis. They state that a noticeable increase in the serum cholesterol content is detected only in the cases in which the disease is of recent onset. In the course of clinical improvements this hypercholesteremia decreases to normal values. If in stationary and slowly progressive conditions improvement is affected by means of treatment, this improvement is usually accompanied by a temporary increase in the cholesterol content. The hypercholesteremia which is observed in the course of new exacerbations or of clinical improvement in cases of chronic multiple sclerosis is regarded as an accompanying symptom or as a part of the defense measures of the organism. J. A. M. A.

Neuropathology

CEREBRAL LESIONS IN HYPOGLYCEMIA. A. B. BAKER, Arch. Path. **26**:765 (Oct.) 1938.

In a previous publication, Lufkin and Baker reported the cerebral alterations in 3 cases of hypoglycemia. They found that the alterations of the nerve cells were of no apparent pathologic significance. The most common pathologic observations were numerous new and old hemorrhages scattered throughout the brain tissue.

On the basis of his present studies, Baker divides the lesions associated with hypoglycemia into three large groups: 1. Cerebral petechiae. These vary from small, discrete extravasations scattered irregularly throughout the brain substance to large hemorrhages that tear into the surrounding tissues and produce definite cerebral damage. 2. Large areas of encephalomalacia, demyelination and cyst formation. 3. Diffuse, generalized glial proliferation and extensive gliosis around the areas of softening.

It is apparent that any single one or any combination of these cerebral alterations is sufficient to produce severe, lasting injury of the brain, permanent functional damage or death. WINKELMAN, Philadelphia.

EXPERIMENTAL PRODUCTION OF TUMORS IN THE BRAINS OF WHITE RATS. ARTHUR WEIL, Arch. Path. **26**:777 (Oct.) 1938.

Weil attempted to study the blastogenic properties of lard solutions and cholesterol combinations of dibenzanthracene, of methylcholanthrene and of the more recently discovered styryl 430 (2 [p-aminostyryl] 6 [p-acetylaminobenzoylamino] quinoline methoacetate). This substance, which had been originally synthesized for combating trypanosomal infections, produced large tumors when injected subcutaneously into rats. These tumors developed from the original phagocytic tissue and appeared as pleomorphic sarcomas.

Injections of dibenzanthracene and lard, of methylcholanthrene and lard and of lard resulted in the production of a granuloma. Injections of lard alone produced the same marked reaction as combinations of lard with dibenzanthracene and methylcholanthrene. The effect did not seem to be more intense in the last experiments than in the case of the lard controls. In only 1 rat could the tumor formation be attributed to the specific effect of dibenzanthracene. Experiments

with injections of styryl 430 produced more uniform and specific results. The results of the experiments with this substance showed that each tissue which came in contact with the dye formed its own specific neoplasm; the subcutaneous tissue, sarcoma; the glia, glioblastoma; the pia-arachnoid, meningioma, and the ependymal lining of the ventricles, the tumors peculiar to these structures.

WINKELMAN, Philadelphia.

BROWN-SÉQUARD SYNDROME. J. B. GAYLOR and J. W. HOWIE, J. Neurol. & Psychiat. **1**:301 (Oct.) 1938.

Gaylor and Howie report a rare case in which a hypernephroma gave rise to a spinal intramedullary metastasis without involving the spinal coverings. The location of the tumor in the right half of the eighth and ninth dorsal segments produced a syndrome closely resembling the pure form described by Brown-Séquard. It differed from the classic syndrome in that there were an extensor plantar response and loss of vibratory sense on the left, although the postural sense on that side was retained.

N. MALAMUD, Ann Arbor, Mich.

THALAMIC HYPERTROPHY OR GLIOMATOSIS OF THE OPTIC THALAMUS. S. NEVIN, J. Neurol. & Psychiat. **1**:342 (Oct.) 1938.

Gliomas of the optic nerves, brain stem and thalamus frequently give rise to general hypertrophy of the area involved rather than to a localized tumor formation. Nevin reports 3 such cases in which the optic thalamus was predominantly involved. In all the cases the growth spread beyond the thalamus either into adjacent parts of the cerebral cortex or into the brain stem. The cells consisted of a wide variety of spongioblastic and astrocytic neuroglia elements in various stages of differentiation and tended to assume a different character in the gray and in the white matter. Because of these characteristics, Nevin considers the pathologic process to be a diffuse gliomatosis of blastomatous origin rather than a true tumor formation. In the 3 cases were all stages of blastomatous overgrowth of neuroglia cells, from hypertrophy of practically normal cells to the focal formation of a small neoplastic area. The author believes that other types of gliomas may arise on the basis of a primary diffuse gliomatosis and that all gliomas should be studied primarily as biologic abnormalities of the neuroglia.

N. MALAMUD, Ann Arbor, Mich.

CREUTZFELDT-JAKOB DISEASE. JAN JANSEN and G. H. MONRAD-KROHN, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:670 (Oct.) 1938.

In 1921 Jakob described spastic pseudosclerosis, which Spielmeyer later called Creutzfeldt-Jakob disease. During the past two decades 14 cases of this type have been reported. There has been recent discussion regarding the need for creating this disease as an entity. A new case is now recorded, that of a man aged 42 who had had a syphilitic infection at 22 and who became sick with influenza during Christmas 1933, one and one-half years before his death. He was in the hospital for three days, when the Wassermann reactions of the blood and spinal fluid were negative. After this febrile illness he became sleepless and anxious and apparently had auditory hallucinations. Weakness in the lower limbs appeared soon after. During April 1934 there developed mild lateral nystagmus on looking to the left; the pupils were somewhat irregular and reacted sluggishly to light; the jaw deviated to the right; dysarthria and a perioral tremor were present. Rigidity and weakness with a positive Babinski sign were found in the lower limbs; the gait was spastic and ataxic, and there was diminished vibration sense in the lower limbs. During the next few months intellectual deterioration became evident. Euphoria appeared, with ideas of grandeur and occasional confabulation. A coarse tremor in the right upper limb appeared. During the fall of 1934 ataxia in all limbs increased.

Autopsy showed atrophy of the frontal region. There was marked degeneration of the lateral tracts throughout the length of the spinal cord. The changes had no relation to the blood vessels. There was extensive dropping out of ganglion cells throughout the cerebral cortex, especially in the deeper layers. Many of the remaining cells showed signs of degeneration. Fatty degeneration in the cells was noted particularly in the frontal and hippocampal regions. Compound granular cells were observed only in the cortex of the hippocampus. Marked astrocytic gliosis accompanied the parenchymatous degeneration, especially in the deeper layers of the cortex. The frontal region, the temporal lobes and the insula were most severely affected. The Betz cells showed marked changes. The other parts of the cortex were much less severely involved. The occipital lobes showed only gliotic changes in the lamina zonalis. The corpus striatum, pallidum and thalamus showed similar changes, except that the cells showed more pallor, swelling and fatty degeneration. Gliosis was especially marked in the pallidum and the thalamus. There was a focal accumulation of gitter cells in the left globus pallidus. In the globus pallidus on both sides lipoid substance was observed free in the intercellular tissue. Glial rosettes were scattered throughout the cerebral white matter. There was degeneration of the white substance in the central regions; scattered gitter cells were seen deep in the white matter of the subcortex and in greater numbers in the fornix, corpus callosum and internal capsules. The pons and medulla showed marked macrogliosis, with some degeneration of the pyramidal tracts. In addition to the severe degeneration of the pyramidal tracts in the cord, the spinocerebellar tracts were involved. Gliotic foci were scattered throughout the cord. The anterior horn cells showed degeneration. Except for mild perivascular lymphocytic infiltration around a few small vessels of the pons and medulla, there was no evidence of inflammation. The meninges were intact.

The Creutzfeldt-Jakob disease is a degenerative disease involving the extrapyramidal and pyramidal systems, the spinal cord and the cerebral cortex. It is usually encountered in patients of from 20 to 55 years of age, and especially in the fourth and fifth decades. The onset is insidious and the duration from a few months to two or three years. The average duration is one year. Remissions have been observed. The disease is usually characterized by a prodromal period of so-called neurotic complaints, such as anxiety, depression, loss of interest, irritability and insomnia. Weakness in the lower limbs and dysarthria are sometimes noted early in the course. Examination of the patient when the disease is moderately advanced shows signs of involvement of the pyramidal and extrapyramidal pathways: tremors, rigidity, dysarthria and disturbances of gait. Deviation of the tongue, facial weakness and other evidence of impairment of the motor cranial nerves may be present. Euphoria, emotional instability, memory and attention defects, psychomotor restlessness and other mental changes appear. These mental changes gradually increase in severity, with a terminal picture of severe dementia.

SAVITSKY, New York.

Psychiatry and Psychopathology

HYSTERICAL BLINDNESS IN CHILDREN. ERNST WOLFF and GEORGE S. LACHMAN, Am. J. Dis. Child. **55**:743 (April) 1938.

Wolff and Lachman report 2 cases of hysterical blindness in children. The first case was that of a girl aged 12 with an intelligence quotient of 72. She showed progressive improvement, with complete recovery. In this case short psychotic episodes were described. These disappeared after treatment and did not recur. The only therapy was a change of environment. The second case was that of a girl aged 8½, with an intelligence quotient above normal, who presented progressive loss of vision. The resulting visual acuity was 10/200 in the right eye and 2/200 in the left eye. A discussion of her situation, particularly of her emotional attitude toward a brother who was about to be married, resulted in complete relief from her symptoms.

WAGGONER, Ann Arbor, Mich.

MENTAL SYMPTOMS OF PELLAGRA: THEIR RELIEF WITH NICOTINIC ACID. T. D. SPIES, C. D. ARING, J. GELPERIN and W. B. BEAN, Am. J. M. Sc. **196**:461 (Oct.) 1938.

Spies and his colleagues observed 60 pellagrins with acute psychoses and other manifestations of pellagra, 15 pellagrins with no mental symptoms but with characteristic dermatitis, glossitis, stomatis and gastrointestinal involvement, 424 patients with subclinical and mild pellagra who have been subject to one or two annual recurrences of the disease, 26 patients with psychoses of other types and 129 pellagrins who had had one or two recurrences of their "neurotic" symptoms each "pellagra season" since the onset of the disease. Patients with subclinical pellagra are noted for the multiplicity of their complaints, among which are many usually classified as neurasthenic. The most common of these symptoms are fatigue, insomnia, anorexia, vertigo, burning sensations in various parts of the body, numbness, palpitation, nervousness, a feeling of unrest and anxiety, headache, forgetfulness, apprehension and distractibility. The conduct of the pellagrin may be normal, but he feels incapable of mental or physical effort, even though he may be ambulatory. The studies suggest that nicotinic acid in adequate amounts is a specific therapeutic agent for the acute mental symptoms of pellagra. Both spontaneous and induced psychoses of pellagra respond promptly to this therapy. Coramine, the diethylamide of nicotinic acid, also is beneficial in the treatment of the abnormal mental symptoms. The psychoses present in 26 nonpellagrous persons did not improve after the ingestion of these drugs. The so-called prodromal or neurotic symptoms of pellagra usually disappear after the administration of nicotinic acid. The studies were conducted in such a manner that suggestion was eliminated, and they indicate that the vague, subjective, prodromal symptoms are evidence of disordered function. Frequently repeated large doses of nicotinic acid prevent the development of mental symptoms in patients with subclinical and with mild pellagra. The minimal dose of nicotinic acid has not been determined, but seems to vary from patient to patient. It is tentatively recommended that each patient with severe mental symptoms receive a total of at least 500 mg. daily. It is preferable to give this in ten doses. In the extremely severe forms convalescence seems to be shortened by the administration of 1,000 mg. daily. Since nicotinic acid is only one of the essential chemical substances present in the well balanced diet, all patients with pellagra should be given a well balanced diet whenever possible, even though nicotinic acid is used as a supplement.

EDITOR'S ABSTRACT.

ANOREXIA NERVOSA AND PITUITARY CACHEXIA. W. J. BRUCKNER, C. H. WIES and P. H. LAVIETES, Am. J. M. Sc. **196**:663 (Nov.) 1938.

The authors describe the cases of 2 girls aged 16 and 18, respectively, with extreme cachexia who regained normal health by increase in food intake without hormonal therapy. The weight of the first patient had fallen from 92 to 50 pounds (41.7 to 22.7 Kg.) in a year. She had practically no appetite. There was loss of pubic and axillary hair in the four months before study, and the menstrual periods, previously regular and normal, ceased abruptly three months before admission. Physical examination revealed findings concomitant with severe cachexia. The psychiatric opinion was that there was nothing to suggest hysterical anorexia, but after the beginning of recovery a history of emotional disturbances prior to the illness was elicited. Treatment in the hospital was directed chiefly toward encouraging the patient to eat. Six months after admission to the hospital there was a striking healthful change in appearance, with increase in weight up to 90 pounds (40.8 Kg.). The second patient, who voluntarily reduced her food intake because of difficulties with her family, showed a loss in weight from 109 to 58 pounds (49.4 to 26.3 Kg.). There were loss of appetite, weakness and constipation; nine months before admission the menses ceased abruptly. Physical examination revealed a picture of extreme emaciation. Detailed psychiatric study of

the patient revealed a psychopathic personality of hysterical type, with normal mental status and a strong mother-daughter attachment. One period of hospitalization was unsuccessful, but the second brought results, with increase in food intake and gain in weight to 121.5 pounds (55.1 Kg.). MICHAELS, Boston.

INCIDENCE AND FUTURE EXPECTANCY OF MENTAL DISEASE. H. F. DORN, Pub. Health Rep. **53**:1991 (Nov. 4) 1938.

Dorn points out that it is commonly believed that the proportion of the population suffering from mental disease is increasing. For the country as a whole the number of persons hospitalized for mental disease increased more than 40 per cent from 1926 to 1936. The most common explanation for the apparent increase in the incidence of mental disease is the complexity and strain of metropolitan life. Owing to the fact that there is no sharp line of demarcation between normality and abnormality, it is practically impossible to decide whether or not the relative number of persons with mental disease is increasing. Fundamentally, mental disease is a cultural concept and varies from one group to another. In some situations the mentally deranged have become soothsayers, medicine men, prophets or group leaders; in other situations the same persons would be incarcerated. From an analysis of the first admissions to hospitals for mental disease in Massachusetts, New York and Illinois, the common belief in this increase is not borne out. The number of first admissions per hundred thousand of population decreased for women under 70 years of age in each state. In Massachusetts the same was true for men. In New York and Illinois commitment rates decreased for the younger age groups, but after 45 or 50 years of age an increase occurred. Nevertheless, mental diseases constitute an important health problem. Unless there is a decrease in the first admission rates to hospitals for mental disease, from 110,000 to 120,000 of the 2,144,800 infants born during 1936 will eventually be committed to a hospital for such disorders. This number excludes the emotionally unstable and unbalanced persons who should be included in a comprehensive mental hygiene program. Owing to the increasing proportion of the population in the older age groups and the increase in life expectancy, an increase in the number of persons hospitalized for mental conditions is to be expected, since rates for mental disease are highest at the older ages. Assuming that the commitment rates for mental disease for the whole United States are no greater in 1960 than they were in New York state from 1929 to 1931, inclusive, it is estimated that about 135,000 persons will be committed annually to a hospital for such disorders for the first time. This is nearly twice the present number of first commitments. J. A. M. A.

HOMESICKNESS AND IMMIGRANT PSYCHOSES: AUSTRIAN AND GERMAN DOMESTIC SERVANTS THE BASIS OF STUDY. I. FROST, J. Ment. Sc. **84**:801 (Sept.) 1938.

In the space of six years Frost saw 40 Austrian and German domestic servants suffering from mental disorders. Homesickness combined with loneliness and exhaustion comprises the principal etiologic factor producing psychoses among immigrants. Hereditary elements do not figure prominently. Mistakes of identity are common, and illusions of resemblance appear to follow the stratifications peculiar to primitive notions of kinship. The forms of mental disorder encountered in the present series of cases comprise acute confusional states, acute schizophrenic conditions, paraphrenia and involutional forms. Rarely reactive depressive and twilight states occur. Endogenous manic-depressive psychosis is rarer still. Bodily reactions may be seen in all the aforementioned forms; loss of appetite, toxemia and vegetative-nervous changes are most common and are most likely to be found in the acute confusional and acute schizophrenic types of disorder.

EDITOR'S ABSTRACT.

EFFECT OF INDUCED HYPERCALCÆMIA ON EXCESSIVE PSYCHOMOTOR ACTIVITY. T. M. CUTHBERT, Lancet **2**:612 (Sept. 10) 1938.

There is evidence that when increased nervous excitability exists induced hypercalcemia exerts a sedative effect. Cuthbert induced hypercalcemia in 19 patients showing increased excitability. Six patients received 4 Gm. of calcium lactate and 6,300 international (U. S. P. XI) units of vitamin D daily. The dosage of parathyroid extract was regulated by frequent estimations of the blood calcium and varied from 10 to 110 units. Eleven patients were given 6 Gm. of calcium lactate, 6 ounces (186 Gm.) of lactose (an attempt to promote intestinal acidity), 9,400 international (U. S. P. XI) units of vitamin D and from 4 to 6 Gm. of ammonium chloride. Injections of parathyroid extract were given every four hours and later every six or eight hours, for from three to sixteen days. The efficiency of the medicinal therapy alone, without parathyroid extract, in promoting hypercalcemia was observed in 2 patients. Eight patients were discharged within nine months of treatment; this proportion was much higher than the hospital rate of discharge for the year. Eight other patients were greatly improved. A good response was obtained in nearly three fourths of the patients treated. The remissions arising with and after treatment were definitely longer than any spontaneous remissions before treatment, with 1 exception. When the percentage rise in blood calcium was more than 30 the period of maximal response was generally under ten days; when improvement commenced below this level the maximal response was more prolonged; thus, if a rise of from 20 to 30 per cent in the blood calcium is obtained improvement follows. The only undesirable effects observed were drowsiness in 1 patient on the tenth day and vomiting in another, probably due to acidosis. Treatment did not have to be curtailed because of these symptoms. The results suggest that once the activity of the parathyroid is stimulated, it persists for some time—from two to six weeks at least. Treatment was found most effective in the absence of hallucinosis. Some patients became resistant to parathyroid extract after heavy doses for about twelve days. Results suggest that in future treatment prolonged intensive medicinal therapy should be tried first; if a more rapid result is desired parathyroid extract should also be given intramuscularly every four hours, the patient receiving about 150 units daily until improvement begins. The injections may then be given less frequently and smaller doses used. Every effort must be made to utilize the resulting period of remission, and the patient's fullest cooperation should be obtained. EDITOR'S ABSTRACT.

HOW A HUNGARIAN GIRL AGED 7 LEARNED FRENCH. A. KENYERES, Arch. de psychol. **26**:322, 1938.

Detailed study of the language of a Hungarian girl who had moved with her parents, and for whom a journal was kept, showed that the strongest motivation for learning French came from a desire to play with her fellows. After six months she was using French and Hungarian to supplement each other, and after ten months she spoke French like a Swiss girl of her age, except for a few difficult verb forms. The learning of French differed significantly not only from normal learning of the use of the mother tongue but also from adult learning of foreign languages. The addition of a second language did not noticeably retard intellectual development. HERRICK, Philadelphia.

GLAUCOMA OF JOY AND OF FEAR. G. OURGAUD and JEAN-SÉDAN, Rev. d'oto-neuro-opht. **16**:548 (Oct.) 1938.

It has long been known that violent emotions influence the incidence of glaucoma. During the bombardment of Paris during the World War, 7 cases of glaucoma occurred in one hospital, containing 1,500 wounded men. These cases occurred only among bedridden patients. In the ambulant patients a certain autodefense attenuated the violence of the nervous shock. Five case histories of patients with acute glaucoma caused by joy or fright are recorded. In all the influence

of psychic states on the physical structure was demonstrated. In all a basis of arterial hypertension, sudden and violent onset of the disease and inconstancy of bilaterality were presented.

DENNIS, San Diego, Calif.

PSYCHOPATHOLOGIC CHANGES ASSOCIATED WITH LESIONS OF THE DIENCEPHALON. G. E. STÖRRING, Arch. f. Psychiat. **107**:786 (March) 1938.

Störring discusses the question of psychopathologic changes associated with lesions of the diencephalon. He reports 3 cases, the first that of a patient who showed signs of encephalitis while convalescing from an attack of typhoid. The neurologic findings pointed to definite involvement of the thalamus and hypothalamus, with unilateral hyperpathia and disturbances of stereognosis, deep sensibility and motor functions, as shown by the typical "thalamus hand." There were visual disturbances, spontaneous pains and paresthesias and optic and haptic hallucinations. In addition, there were changes in the sleep rhythm, involvement of the bladder, hyperthermia and excessive perspiration, all of which pointed to a lesion of the hypothalamus. There were no signs of definite cerebral or cerebellar involvement. Psychopathologically, in addition to the hallucinations and sensory disturbances, there were fluctuations in the emotional and affective fields, particularly in reaction to peculiar sensory perceptions. There were states of delirious excitement, with fear and overactivity followed by amnesia. There were at times manic-depressive–like fluctuations in mood and at other times performances which were definitely of a hysteroid nature. At no time was there any development of delusional trends. The second case was similar to the first, both in symptoms and in probable pathologic changes. In the third case, in which symptoms pointing to a lesion of the diencephalon developed as a sequel to encephalitis lethargica, there was, in addition to the preceding disturbances, a definite trend toward schizophrenic organization in the form of a delusional system.

W. MALAMUD, Iowa City.

SCHIZOPHRENIA IN ITS RELATION TO SEX, AGE AND SEASONAL VARIATIONS. M. HAAS, Arch. f. Psychiat. **108**:552 (July) 1938.

Cases of all patients with schizophrenia admitted to hospitals in the period from 1924 to 1933 were reviewed for the purpose of determining the relations of schizophrenia to sex, age and season. Haas analyzed 5,229 cases of schizophrenia. The proportion of male schizophrenic patients to the total male population was 15.3 per cent, whereas the proportion of female patients was 27.8 per cent, showing a marked relative predominance of schizophrenia in the latter. Further analysis on the basis of first admissions showed that there was also an absolute predominance of female over male patients, there being 123 women and 100 men. More or less similar findings were reported from the Heidelberg and from the Zurich clinic. This is in apparent contradistinction to reports from the New York hospitals, where males were found to be predominant. The age on admission shows that the highest peak in men was at the age of 23 years; in women it was at about the age of 29. In both sexes there was a relatively high frequency between the ages of 45 and 50, but this was much more marked in women than in men. This is in keeping with the fact that the more abrupt onset of the climacterium in women presents a possible etiologic factor for some of the schizophrenias occurring at this age. There is no definite relation between rate of admission and season except that the number of admissions is highest in the summer.

W. MALAMUD, Iowa City.

HEREDITY AND EPILEPSY: V. THE PROBLEM OF EPILEPTOID PSYCHOPATHY. K. CONRAD, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:505 (May) 1938.

The incidence and nature of character and personality disorders were studied in all children aged over 20 of 553 epileptic persons. There were over ten times as many abnormal persons in the idiopathic (77:911) as in the symptomatic

(2:275) group. The explosive and emotional types predominated, constituting about 40 per cent of the psychopathic reactions in the idiopathic group. In Stumpf's study of the siblings of recidivists there were only 20 per cent of this type, and in Riedl's study of the children of psychopathic persons there was only 1 per cent. Pedantry, bigotry, fanaticism, seclusiveness and religiosity were not prominent. Thirteen per cent of the children over 18 of persons with idiopathic epilepsy came into contact with the law, as compared with a normal incidence of 5 per cent. The incidence of delinquency in the idiopathic group was about four times that of the symptomatic group. Most of the crimes resulted from quarrels with people in the immediate environment. Stealing, forgery and embezzlement were less frequent; begging was common. Much of the criminality evidently arose from the marked affective lability of epileptic persons. The suicide rate was 5.7 per cent in the idiopathic group. The control average given by Conrad was 3.2 per cent. The difference is not significant. The suicide rate for the children of persons with idiopathic epilepsy may be explained by the relatively younger age of this group as compared with the controls. Suicidal attempts in this group were usually impulsive and unaccompanied by depression and were not in reaction to an adequate situation.

The author suggests that the term "epileptoid psychopathic" be avoided. He prefers to use the descriptive terms "explosive" and "emotionally labile." The abnormal frequency of the explosive and emotionally labile psychopathic types in a particular family has value in the diagnosis of hereditary epilepsy.

SAVITSKY, New York.

HEREDITARY FACTORS IN MANIC-DEPRESSIVE PSYCHOSIS. ELIOT SLATOR, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:1 (Jan.) 1938.

Slator studied the incidence of manic-depressive psychoses in the parents and children of 138 patients with manic-depressive psychoses. The criteria for inclusion in the series was a first attack of the disease before the age of 50, either one definite manic and one depressive attack or three manic or depressive episodes. The incidence of manic-depressive psychoses in the relatives of patients was 19.7 per cent. A control study of 8,775 cases (in 4,407 of which the patients were women) compiled from the literature showed an incidence of 0.3805 ± 0.1145 per cent. The figures were 11.5 per cent for the parents and 22.2 per cent for the children. The frequency of manic-depressive psychoses in the relatives of patients with cyclothymia is thirty to sixty times that of the control figures. Schizophrenia was found in 0.8 per cent of the parents and in 3.1 per cent of the children. Because of the small number of cases and the probability of wrong diagnoses, the author does not believe that the last figure is significant. Manic-depressive features were noted in the 4 parents and 9 children who were schizophrenic.

SAVITSKY, New York.

Diseases of Brain

CONVULSIONS COMPLICATING PERTUSSIS. K. HABEL and P. F. LUCCHESI, Am. J. Dis. Child. **56**:275 (Aug.) 1938.

Habel and Lucchesi discuss the clinical features peculiar to convulsions occurring in 41 of 516 patients with pertussis. The factors predisposing to convulsions included the age (less than 2 years) of the patient, the severity of the paroxysms and the presence of cyanosis, bronchopneumonia and congenital defects of the brain. The mortality rate for the series was 78 per cent, but for 17 patients to whom transfusions were given the death rate was 35 per cent. In the majority of cases no specific pathologic change was present in the brain to point to an essential inflammatory cerebral disease as the etiologic agent; there were, rather, changes that must be attributed to an insufficient blood supply and to anoxemia. Clinically,

convulsions usually occur in the spasmodic stage of the disease, when the paroxysms are severe. This frequently results in venous congestion of the head and neck, with severe anoxemia. In patients having convulsions when pertussis is complicated by bronchopneumonia, cyanosis and inefficient circulation are instrumental in producing cerebral anemia and anoxemia. Since pertussis convulsions are most likely to occur during the whooping stage and to follow a paroxysm, any therapeutic measure that will reduce paroxysms to a minimum may be considered a prophylactic agent. The authors believe that cyanosis is a responsible causative factor; therefore oxygen should be used early in all cases of bronchopneumonia and of severe paroxysms even in the absence of bronchopneumonia. Once convulsions have begun, barbiturates should be given by mouth, by rectum or by the subcutaneous route. This should be supplemented with an immediate transfusion of whole blood and with the administration of oxygen (by means of a tent rather than by catheter). Tight bandaging of the extremities seems to help in a few cases. Attempts to overcome cerebral anoxemia should also include treatment to decrease the cerebral edema. Concentrated lyophilic normal human serum seems indicated, because theoretically it will dehydrate the cerebral tissue as well as increase the blood pressure and help to overcome vasomotor collapse.

EDITOR'S ABSTRACT.

EASTERN EQUINE ENCEPHALOMYELITIS: HISTOPATHOLOGY OF NERVOUS SYSTEM IN GUINEA PIG. L. S. KING, J. Exper. Med. **68**:677 (Nov.) 1938.

King studied the neuropathologic features of equine encephalomyelitis in the guinea pig. After peripheral inoculation the earliest detectable pathologic change is the accumulation of leukocytes within the lumen of the blood vessels and the proliferation of the vascular adventitia. This precedes the appearance of any significant perivascular cuffing and may or may not be accompanied by a few polymorphonuclear leukocytes. The typical lesion is a fairly well circumscribed focus of polymorphonuclear leukocytes accompanying the vascular changes. The leukocytes may be numerous or sparse and may or may not be accompanied by destruction of neurons. The neocortices and olfactory cortices are the principal sites of predilection. A distinction between inflammatory and degenerative lesions depends on the relation between the neuron destruction and the exudative changes. After intracerebral inoculation the inflammatory changes are much less marked than after peripheral inoculation. This is due to a difference in type of pathologic process. After intracerebral inoculation there is primary destruction of neurons, involving especially the hippocampus and also large areas of the neocortex. This change, similar to ischemic necrosis, is regarded in part as a nonspecific reaction of especially vulnerable tissue.

J. A. M. A.

A CASE OF APHASIA, WITH SPECIAL REFERENCE TO THE PROBLEMS OF REPETITION AND WORD-FINDING. K. GOLDSTEIN and J. MARMOR, J. Neurol. & Psychiat. **1**:329 (Oct.) 1938.

Goldstein and Marmor report an unusual case of amnesic aphasia following a cerebral insult. The outstanding features were change in personality, with loss of the capacity for abstract conception, and striking impairment in the naming of objects and in the ability for repetition, although there was relative retention of the capacity for speech and understanding. The anatomic changes suggested that this loss of the capacity for repetition and word finding was caused by lesions in the left island of Reil and in the adjacent convolutions of the left temporal and parietal lobes, corresponding to the patient's right handedness. According to Goldstein, the special capacity for repetition is dependent on a complex association system, localized in the cortex of the island of Reil. The retention of the expressive and the receptive function of speech was explained by the intactness of the left third frontal convolution and the right temporal lobe, respectively.

The selective impairment of the capacity for word finding and repetition is also related to the change in personality, with its concreteness of behavior, characterizing patients with amnesic aphasia. N. MALAMUD, Ann Arbor, Mich.

PARALYSIS OF THE EXTERNAL PTERYGOID MUSCLE ARISING FROM INJURY TO THE FIFTH CRANIAL NERVE. H. GARDINER, Lancet **2**:428 (Aug. 20) 1938.

Three cases are reported of paralysis of the external pterygoid muscle and sensory involvement of the trigeminal nerve resulting from a severe blow to the right side of the face, with accompanying loss of consciousness of shorter or longer duration. In each instance the whole second division of the fifth nerve was involved. Fracture of the base of the skull was demonstrated in only 1 case. Hemorrhage into the pterygoid muscle may account for the defect, but is unlikely. The damage to the nerves is probably near the foramen rotundum and the foramen ovale. Injury to the nerve to the pterygoid muscle from the third division and the sensory impairment from a lesion of the second division are thus explained, especially since fracture of the base of the skull was proved in 1 case and surmised in the other. Only 1 of the patients did not recover even after a period of nineteen months.

KRINSKY, Boston.

NONTRAUMATIC INTRACEREBRAL HEMATOMA. L. LARUELLE and L. MASSION-VERNIORY, J. belge de neurol. et de psychiat. **38**:495 (July) 1938.

Nontraumatic intracerebral hematoma occurs infrequently; its pathogenesis is frequently not determined. The differentiation of hematoma and cerebral tumor may be difficult. Laruelle and Massion-Verniory report the case of a nontraumatic hematoma in the right frontoparietal area in a man aged 42 which was cured by operation and state that treatment of disorders of this type is exclusively surgical.

DE JONG, Ann Arbor, Mich.

CONCURRENT FACTORS IN THE GENESIS OF NERVOUS DISEASES. HENRY MARCUS, Confinia neurol. **1**:230 and 285, 1938.

Marcus discusses the theory of multiple causation of diseases of the nervous system. He states that two pathologic factors which simultaneously affect the organism may bring about definite disease entities. He believes, for instance, that influenza plays an important part in producing diseases of the nervous system by causing a latent infection which, in combination with some other infection, such as syphilis, may precipitate nervous disease. The virus of influenza may combine itself with or activate a syphilitic infection. Lethargic encephalitis, which the author considers to be a manifestation of influenza, contributes to the development of many widely varying diseases of the nervous system, such as multiple sclerosis, syringomyelia, progressive muscular atrophy, amyotrophic lateral sclerosis, hemiplegia, epilepsy and psychoses. Alcohol may be of importance in precipitating diseases of the nervous system; an acute alcoholic delirium may develop during the course of pneumonia, gastritis or nephritis, or Korsakoff's disease may be brought on by the simultaneous effects of alcohol and an acute or chronic infection. Neuroses frequently develop in close relation with organic disease processes, especially infections, cachectic states or endocrine disorders. Trauma may be a factor in precipitating latent disease processes. The possibility of multiple factors must always be considered in the study of nervous diseases, and the individual factors must be evaluated.

DE JONG, Ann Arbor, Mich.

NEUROLOGIC SYNDROMES OF RECKLINGHAUSEN'S NEUROFIBROMATOSIS. F. VIZIOLI and S. TOLONE, Riv. di neurol. **11**:281 (Aug.) 1938.

Vizioli and Tolone report 4 cases of diffuse neurofibromatosis of Recklinghausen's type. In the first case the neurologic symptoms were those of an intramedullary tumor at the cervical segment of the spinal cord with formation of

intratumoral cavities of the syringomyelic type. The second patient showed cerebral symptoms from bilateral multiple neurofibromas of the posterior cranial fossa. He had a nodule in the right laterocervical region, which for the last few months had been painful on pressure and had developed rapidly. The nodule was removed. It was found that it had been transformed into sarcoma of the neurofibromatous type, which does not produce metastases. The third patient had suffered in childhood from a nervous disease (either polyneuritis or poliomyelitis) from which there were residual left facial paralysis and atrophic paralysis of one leg. He showed symptoms of compression of the cervical segment from an extramedullary tumor which seemed to originate in the distal roots of the right cervical nerves. The fourth patient had complete spastic paraplegia with contracture in flexion from spinal trauma. The neurologic syndrome consisted in complete flaccid paralysis of the left arm from compression of the brachial plexus by a large fibrosarcoma deeply seated in the axillary cavity. The patient had an associated incomplete acromegalic syndrome. The authors made a microscopic study of the tumors removed at operation, of the cutaneous nodules and of some neurofibromas, taken for biopsy in all but the first case, which was the most simple. They observed that the cutaneous nodules and an extramedullary tumor had the typical microscopic aspect of neurofibromatosis of Recklinghausen's type. The tumor showed sarcomatous degeneration in 2 cases. Some oligodendroglia cells of the first (Robertson) and second (Cajal) types were identified in the preparations of neurofibroma. In connection with the cases reported, the authors discuss the pathogenesis of neurofibromatosis of Recklinghausen's type, which they believe originates in defective development of the nervous system during embryonic evolution. The endocrine disorders that precede or are associated with the disease are secondary factors.

EDITOR'S ABSTRACT.

OPHTHALMOSCOPIC SIGN OF INTRACRANIAL HYPERTENSION. J. PEREYRA KÄFER, Rev. Asoc. méd. argent. **52**:835 (Aug. 30) 1938.

The sign described by Pereyra Käfer is seen during ophthalmoscopic examination of the fundus of the eye. It consists in the diminution or absence of changes of the retinal venous circulation which are caused by bilateral compression of the jugular veins in the neck of normal persons. The changes consist in an increase of the caliber and darkening of the color of the retinal veins and diminution of the venous pulsation up to complete stopping as compression advances, and the energetic venous pulsation suddenly returns after sudden decompression (negative sign). The retinal circulatory changes do not take place in the presence of intracranial hypertension (positive sign). The author makes the examination with an ophthalmoscope for direct vision on the patient seated. An assistant, who stands behind the patient, performs bilateral compression of the jugular veins and subsequent sudden decompression in the course of the examination. The author obtained a negative response in 100 normal persons and a positive response in many cases of intracranial hypertension, 15 of which are reported. He says that the diminution or lack of response in cases of intracranial hypertension depends on the presence of hypertension of the retinal veins, which develops earlier than edema of the optic disk. The sign is positive in association with intracranial hypertension of any origin. It appears earlier than edema of the disk and is reliable. When intracranial hypertension subsides, the sign changes from positive to negative.

EDITOR'S ABSTRACT.

EPILEPTIFORM ATTACKS DURING INSULIN THERAPY OF SCHIZOPHRENIA. G. GROSS-MAY, Nervenarzt **11**:400 (Aug. 15) 1938.

Gross-May says that of 105 schizophrenic patients who were subjected to insulin therapy, 37 had one or more epileptiform attacks in the course of the treatment. The occurrence of these attacks showed no dependence on the age and sex of the patient nor relation to the dose or type of insulin or to the blood

sugar content or the atmospheric conditions. On the other hand, it cannot be ruled out that epileptic heredity produces predisposition. However, the author emphasizes in this connection that there are considerable clinical differences between a true epileptic attack and the epileptiform hypoglycemic crisis. On the basis of the time of appearance of the attack, she differentiates two groups of patients, those with early and those with late epileptiform attacks. In the first group, the attacks developed between the second and the third half-hour after the injection of insulin; in the second group, between the second and the fourth hour. In women the relatively early attacks are more frequent; in men, the late attacks. In evaluating the therapeutic significance of the epileptiform attacks, the author says that the results are somewhat better in patients in whom these attacks develop than in those in whom they do not. However, this more favorable prognosis is explained partly by the fact that the duration of the schizophrenia was on the average shorter in the persons who reacted with epileptiform attacks. If an attack is immediately followed by improvement the prognosis is favorable. In some cases the attack may be followed by an exacerbation. In cases in which the attacks occur early the danger of somatic damage is slight, but in the cases in which they appear late measures should be taken immediately to prevent such damage. If, however, attacks are desired for therapeutic reasons, the insulin shock therapy should be combined with metrazol treatment.

EDITOR'S ABSTRACT.

INSULIN INTOXICATION. G. W. KASTEIN, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:322 (Aug.) 1938.

A woman aged 32 had been hospitalized for an acute catatonic episode for six years. She recovered sufficiently in six months to return to work as a schoolteacher. She was readmitted for a recurrence of catatonic symptoms and was given seventy-five doses of insulin. Coma resulted sixty times. A total of 9,600 units was administered. The first coma appeared after 160 units. On one occasion, after a period of freedom of ten days, only 70 units was needed to induce shock. The patient remained comatose for twenty days after the seventy-fifth injection (160 units) until death. The increased sensitivity to insulin after a period of freedom is due to the absence of the hypophysial anti-insulin hormone, production of which is apparently stimulated by injections of insulin. Kastein found a mild diminution of sodium chloride in the blood during hypoglycemic coma and a tendency for the sodium chloride in the red cells to pass into the blood plasms. The values for blood sugar during prolonged coma showed marked variations, but were not low. On certain days even hyperglycemia was noted. The facts that coma may appear after adequate feeding of dextrose and the presence of normal and high values for blood sugar during coma indicate that there are factors other than hypoglycemia which account for the persistent insulin coma. A direct action of the insulin on neural tissue must be postulated.

SAVITSKY, New York.

OBSERVATIONS AND SYMPTOMS IN CASES OF TEMPORAL AND OCCIPITAL TUMORS. A. TORKILDSEN, Norsk mag. f. lægevidensk. **99**:996 (Sept.) 1938.

Torkildsen analyzes 17 cases of tumor in the temporal lobe and 9 of tumor in the occipital lobe in his series of 154 cases of verified tumors of the brain. The patients were mostly adults; the youngest was 13, the oldest, 56. The most important subjective symptoms were, in order: headache; vomiting; visual disturbances, in the patients with occipital tumor, and focal epilepsy in those with temporal tumor. Mental disturbances, which occurred in 11 of the first group and in 7 of the second, were seldom noted by the patients with occipital tumor, but oftener by those with temporal tumor. All the patients with occipital tumor but 1, who was blind, had defects in the visual field, but only 2 realized the fact. The change first appeared in the lower quadrant. Homonymous hemianopic

changes were not recorded in the patients with temporal tumor. Sensory changes were rare. Symptoms of motor deficiency were not infrequent in the patients with temporal tumor. Cerebellar dysfunction was frequently present, especially in the patients with occipital tumor. In the patient with aphasia, alexia and apraxia the tumor was mainly in the right hemisphere. Calcification atrophy on the same side as the tumor was established in 2 cases of temporal tumor, distention of the porus acusticus on the same side as the tumor in 1 case and intracerebral calcification corresponding to the site of the tumor in 1 case. The albumin content of the cerebrospinal fluid was increased; the cell count was not over 16/3.

EDITOR'S ABSTRACT.

ERRONEOUSLY DIAGNOSED CRANIAL TUMORS. K. H. KRABBE and M. ELLERMANN, Ugesk. f. læger **100**:925 (Aug. 18) 1938.

Of the 18 cases of cranial tumors described by Krabbe and Ellermann, 14 had been diagnosed as vascular disease of the brain, 2 as cerebrospinal syphilis, 1 as epidemic encephalitis and 1 as disseminated sclerosis. In all cases necropsy disclosed tumor of the brain, in the last case coincident with the disseminated sclerosis. The authors find that hemiparesis of acute onset in an older person without signs of choked disk may be due to a multiform glioblastoma in the cerebral hemisphere. If the albumin content is more than 20 mg. and the picture, nevertheless, is that of thrombosis rather than of hemorrhage in the brain, a tumor may be present, and the probability of a tumor is strengthened if the patient is increasingly dull, exhausted and confused. Multiform glioblastomas, however, are usually inoperable. In cases in which there is meningioma there is a certain intermittence in the symptoms, especially at the start; otherwise there is steady progression. When there are chronic extended cerebral symptoms an intracranial tumor is probable; in rare cases of meningioma the start may also be acute and the course rapid. In syphilitic patients with cerebral symptoms the possibility of a tumor should not be overlooked.

EDITOR'S ABSTRACT.

Diseases of Spinal Cord

ACUTE BULBAR POLIOMYELITIS FOLLOWING RECENT TONSILLECTOMY AND ADENOIDECTOMY. M. STILLERMAN and A. E. FISCHER, Am. J. Dis. Child. **56**:778 (Oct.) 1938.

Stillerman and Fischer studied the 686 patients with poliomyelitis who were admitted to the Willard Parker Hospital during 1935 in order to determine whether the removal of tonsils and adenoids in any way influenced the onset or clinical type of the disease. It was found that tonsillectomy and adenoidectomy had been performed in 10 cases during the month antedating the illness. In 8 of these cases poliomyelitis began from ten to twelve days, and in the other 2 cases, sixteen and twenty-two days, respectively, after the operation. Six of 10 patients had the bulbar or encephalitic form of the disease. Careful inquiry was made among 52 patients with poliomyelitis who were admitted to the hospital during 1937. On 3 of these patients tonsillectomy had been performed from two to three weeks preceding the onset of poliomyelitis. These 3 children had the bulbar type of the disease. All of them died. The bulbar or encephalitic type of poliomyelitis was present in 68 of the 686 patients and in 15 of the 52 patients, while in 6 and 3 patients, respectively, who recently had had tonsils and adenoids removed the bulbar or encephalitic type developed. Thus, there was a disproportionately high percentage of bulbar involvement among the tonsillectomized patients in both the 1935 and the 1937 outbreak. This much higher incidence of bulboencephalitic forms suggests the operative field as the port of entry of the virus. The authors conclude, therefore, that tonsillectomy and adenoidectomy should not be encouraged during an epidemic of poliomyelitis.

AUTHOR'S ABSTRACT.

ACUTE ANTERIOR POLIOMYELITIS FOLLOWING TONSILLECTOMY AND ADENOIDECTOMY, WITH SPECIAL REFERENCE TO THE BULBAR FORM. R. C. ELEY and C. G. FLAKE, J. Pediat. **13**:63 (July) 1938.

The fact that the bulbar form of acute anterior poliomyelitis has been reported after tonsillectomy and adenoidectomy has suggested that this procedure may in some manner influence the entrance of the virus. A study of 418 consecutive patients with acute poliomyelitis adds further evidence as to this possibility and strongly suggests that when the operation is elective it may be advisable to postpone it if poliomyelitis is prevalent. Eley and Flake offer the following information in support of this statement: Of 287 patients with spinal poliomyelitis there were only 8 with a history of recent tonsillectomy and adenoidectomy. Of the 8 patients, only 3 acquired the disease between the seventh and the eighteenth day (the commonly accepted incubation period of poliomyelitis) after the operative procedure. Of 131 patients with bulbar poliomyelitis, 17 had had the operation within twenty days prior to the onset of their illness. Fifteen of the 17 patients acquired the disease within the usual period of incubation. Statistical computations demonstrate that the occurrence of this number of cases within the given period cannot be attributed to chance or to the usual frequency of poliomyelitis. The clinical observations suggest that if the patient is harboring the virus at the time of the operation, traumatization of the tissues may enable it to gain entrance to the central nervous system by way of the lymphatic system or the blood stream or perhaps by direct neural extension. The fact that 1 of the patients acquired bulbar poliomyelitis after adenoidectomy without tonsillectomy indicates that it is not necessarily the latter operation which enables the virus to gain entrance to the central nervous system.

J. A. M. A.

SPONTANEOUS HAEMATOMYELIA. J. C. RICHARDSON, Brain **61**:17, 1938.

Hemorrhage into the spinal cord is decidedly rare, as compared with the frequent occurrence of cerebral hemorrhage. The usual conception of hematomyelia is that of a large intramedullary spinal hemorrhage with a tendency to spread longitudinally through several segments. The hemorrhage shows a marked predilection for the gray matter. The posterior horns are invaded more often than the anterior horns.

The causes of hematomyelia are multiple. They include: (1) trauma; (2) spontaneous hemorrhage, as in cases of primary hemorrhage without trauma; (3) secondary hemorrhage, as in cases of syringomyelia, intramedullary spinal tumors, syphilitic myelitis, hemorrhagic diathesis, miliary aneurysm of the spinal arteries and acute myelitis, and (4) accessory hemorrhage—small hemorrhages not giving rise to any clinical symptoms. Arteriosclerosis and hypertension play little or no part in the etiology of hematomyelia. The age incidence of hematomyelia is greatest between 20 and 30 years. Men are much more commonly affected than women.

The present investigation was concerned primarily with the spontaneous type of hematomyelia. Four cases were studied, in 3 of which postmortem examinations were made. The first case was that of a man aged 25 who had a gradual onset of numbness and, later, of weakness of the right leg for four weeks, then sudden severe pain in the legs and back, followed by complete paralysis of the legs, bladder and bowel. Examination suggested a complete transverse lesion of the cord at about the first lumbar segment, with a higher intramedullary lesion from the fifth to the ninth thoracic segmental level. Postmortem examination disclosed a round tubular cavity containing blood clot, which extended from the lower part of the fourth dorsal segment to the lower end of the cord. It was largest at the first lumbar segment. Histologic examination disclosed a small angioma which had ruptured.

Vascular tumors and malformations of the spinal cord are rare, but in the cases reported hematomyelia is not an uncommon complication. Such "angiomas" are

probably developmental vascular malformations rather than true tumors. They tend to occur in either the cervical or the lumbar enlargement. True vascular tumor, or hemangioblastoma, may also occur in the spinal cord, though much less commonly than at its favorite site in the cerebellum. The association of hematomyelia with these tumors is not as well defined as with the angiomatous malformations.

The second case occurred in a man aged 58 with syphilis who, seventeen months previously, had a sudden onset of severe abdominal pain and complete paralysis of the legs, bladder and bowel. He recovered progressively for several months, but marked weakness and rigidity of the legs remained. One year after the onset he began to have more severe pain in the legs. There was no sensory level, but the muscular wasting suggested a lesion as high as the tenth or eleventh thoracic segment. He died twenty months after the onset of symptoms. Postmortem examination revealed an old area of hematomyelia extending from the ninth thoracic to the fourth lumbar segment. Histologic examination revealed definite evidence of syphilitic vascular disease of the small vessels. Syphilis as a cause of hematomyelia seems to be uncommon.

The third case was that of a man aged 31 in whom there developed suddenly severe pain in the neck, radiating to both shoulder blades. There were loss of power of the left arm, paralysis of the urinary bladder and weakness of the left leg. The patient died three weeks after the onset of symptoms. Postmortem examination revealed hemorrhage into the cord on the left side, extending from the third to the seventh cervical segment. Histologic examination was incomplete; no vascular disease or anomaly was demonstrable.

Case 4 was that of a man aged 38 who experienced a sudden onset of pain in the arms, followed by weakness of the hands. This was followed by total paralysis of the hands, right leg and bladder; weakness of the trunk muscles, and subjective sensory loss over the right leg and right side of the trunk. Recovery occurred gradually, with residual weakness and wasting of the upper limbs and spastic weakness of the right leg. The lesion in this case was accurately localized as an elongated, central lesion in the cord, involving the anterior horns in the lower end of the cervical enlargement, spreading down into the posterior commissure and posterior columns and causing a dissociated sensory loss over both sides of the trunk and loss of deep sensation in the legs. It apparently extended into the right lateral column to cause the ipsilateral pyramidal tract signs and the partial contralateral sensory loss due to encroachment on the spinothalamic tract. The sudden onset in a previously healthy man makes one fairly confident of a diagnosis of hematomyelia with persistent cavitation and gliosis of the cord.

The onset of hematomyelia is characteristically sudden. Though symptoms vary with the site of the lesion, there are usually total paraplegia of the legs, a definite sensory level below which all forms of sensation are lost and paralysis of the bladder and bowel. Pain is said to be common, but not invariable. It was a symptom common to all 4 cases reported by the author. The pain is probably of central origin, due to hemorrhage into the posterior horns. The pain disappears with the arrival of complete paralysis. The prognosis in cases of primary hematomyelia is difficult, in view of the several possibilities of the cause of the disease. The cases in which the course is rapidly fatal are chiefly those of hemorrhage into the cervical portion of the cord. No exact figures are available, but it is probable that in a large proportion of cases the disturbance is less severe and does not terminate fatally.

It is generally stated in the literature that trauma is much the commonest cause of hematomyelia. The author believes that traumatic hematomyelia has assumed a false position of importance in the incidence of true hematomyelia. Holmes, in a study of spinal injuries of warfare, was impressed by the fact that hemorrhages were by no means the outstanding pathologic feature of direct injury

to the spinal cord. True hematomyelia was not observed in any of his 15 cases. Jefferson expressed the same opinion. Granted that hemorrhage may occur throughout several segments in a few cases of spinal injury and may well be most marked in the gray matter, the lesion is usually associated with marked softening and is a hemorrhagic softening rather than a pure central blood clot.

The term "spontaneous hematomyelia" is best understood as meaning a primary, nontraumatic, elongated, central hemorrhage of the cord, occurring in the absence of preceding symptoms of a lesion of the spinal cord. It is difficult to conceive of such a hemorrhage as occurring from healthy vessels, and the author takes the view previously emphasized by Brooks that there is always disease of the vessels. In this sense, such hemorrhages are really secondary, but the term "secondary hematomyelia" is better reserved for conditions occurring with tumor of the spinal cord, syringomyelia and myelitis, which in themselves had previously produced symptoms of involvement of the spinal cord. SALL, Philadelphia.

Vegetative and Endocrine Systems

PRECOCIOUS MASCULINE BEHAVIOR FOLLOWING ADMINISTRATION OF SYNTHETIC MALE HORMONE SUBSTANCE. J. B. HAMILTON, Endocrinology **23**:53 (July) 1938.

Hamilton undertook an experiment to differentiate the biologic action of androgenic substance on behavior from any psychologic response due to knowledge of the injection of androgen. He studied 59 chicks, divided into three groups, treated with testosterone propionate. Animals serving as controls received daily injections of 0.1 cc. of peanut oil subcutaneously, and the experimental animals received a similar amount of oil containing 500 micrograms of testosterone propionate. The injections were begun on all chicks on the second day after hatching. It was found in the newly hatched chicks that synthetic androgenic substance caused stunting of body growth and stimulated not only the gross and cytologic growth of organs but also the induction of cocklike behavior. Aggressiveness and crowing appeared in 10 day chicks weighing 68 to 70 Gm. and antedated the development of mature, high-pitched tones. Female chicks were also given injections. Although growth of the comb and wattles was pronounced and the changes in weight were the same as in the males, no crowing, wing flapping or other actions indicative of male behavior were observed during a period of fifty-five days.

PALMER, Philadelphia.

INFLUENCE OF ADRENAL CORTEX EXTRACT UPON COMPENSATORY HYPERTROPHY OF THE ADRENAL CORTEX. E. M. MACKAY and L. L. MACKAY, Endocrinology **23**:237 (Aug.) 1938.

In previous work the authors established that when one adrenal gland is removed the cortex of the remaining gland undergoes hypertrophy. This does not occur if the hypophysis is removed simultaneously. The authors used albino rats (litter mates) of varying weight. The adrenal gland removed surgically served as the control. The degree of compensatory hypertrophy was represented by the increase in weight of the hypertrophied gland above the weight of the normal gland removed at operation. The authors found that the compensatory hypertrophy following removal of one adrenal gland was suppressed or prevented by the administration of extract of adrenal cortex. They propound the theory that the hypertrophy is dependent on stimulation by a hormone of the anterior lobe of the pituitary, the production of which depends on the concentration of the hormone of the adrenal cortex, circulating in the organism.

PALMER, Philadelphia.

CHANGES IN THE HYPOPHYSIS AND THE OVARIES OF RATS CHRONICALLY TREATED WITH AN ANTERIOR PITUITARY EXTRACT. J. B. COLLIP, H. SELYE and J. E. WILLIAMSON, Endocrinology **23**:279 (Sept.) 1938.

The authors treated rats twice daily with 0.04 cc. of a pituitary extract prepared from the acetone-defatted anterior lobe of the pig pituitary. The extract, rich in gonadotropic and thyrotropic principles, was assayed so that 0.01 cc. given three times daily to 21 day old female rats produced ovaries of 44 mg. in seventy-two hours and 0.02 cc. administered twice daily to 200 Gm. guinea pigs produced thyroids of 37 mg. which, on histologic examination, were definitely hyperplastic. The results showed that treatment for from one to twenty-four weeks produced a transient increase in ovarian weight due to the formation of many corpora lutea. This increase reached its peak more rapidly in the adult (2½ month) rat, but in the immature (21 to 30 day) rat the increase was more pronounced and reached a much higher level. Resistance to such treatment therefore develops more rapidly in the adult than in the immature female. In hypophysectomized rats, treated for periods of from one to thirteen weeks, the peak of the curve was somewhat delayed as compared with that in the normal mature or immature animal, but resistance finally developed even in the absence of the hypophysis and the size of the ovary retrogressed. Parallel with the development of ovarian atrophy, "signet ring" castration cells appeared in the hypophysis, and cysts formed in some cases as a result of liquefaction and confluence of these vacuolated cells. At the height of this acquired resistance, the ovary showed such severe atrophy as is observed only in hypophysectomized animals, and the "wheel cells," a characteristic sign of hypophysial deficiency, appeared. These ovaries were resistant not only to the gonadotropic action of the extract but also to implants of rat hypophysis. Both these facts indicated that treatment led to antihormone development, a condition of at least relative immunity to the animal's own hypophysial secretion. This interpretation received further support from an experiment in which massive doses of a gonadotropic preparation from the urine of pregnant women failed to cause maturation of follicles or formation of corpus luteum, but led exclusively to pronounced luteinization of the theca. This is never observed in adult rats treated with such preparations, except after complete surgical removal of the hypophysis.

PALMER, Philadelphia.

UNUSUAL RESULTS FOLLOWING THE INJECTION OF EPINEPHRINE. G. DE M. RUDOLPH, Endocrinology **23**:366 (Sept.) 1938.

Nine patients suffering from dementia paralytica were given subcutaneous doses of from 0.29 to 1.18 mg. of epinephrine hydrochloride at intervals of from seven to thirty-six days, and the pressor and depressor effects recorded by determinations of blood pressure. A consistent decrease of pressor effect was produced by each injection subsequent to the first in all cases. An increase in depressor effect with subsequent injection of the same or larger doses occurred in 8 of 10 experiments. These effects were cumulative, but greater changes did not occur when the interval was longer than seven days.

PALMER, Philadelphia.

THE HYPOPHYSIS IN EXOPHTHALMIC GOITER. C. WEGELIN, Ann. d'anat. path. **15**:703 (July) 1938.

After the discovery of the hypophysial thyrotropic hormone, the theory was advanced that exophthalmic goiter may be due to hypersecretion of this hormone. Wegelin studied the hypophysis in 20 cases of this disease, but in none of them did he find evidence of hyperfunction of the anterior lobe. The outstanding change was always more or less pronounced pericapillary edema with marked hyperemia. Degenerative changes, in the form of diffuse swelling or complete degeneration,

were observed in the three types of cells of the anterior lobe. The injection into a guinea pig of acetone extract of the hypophysis from a patient with exophthalmic goiter did not change the epithelial lining of the thyroid gland. The injection of the extract of a normal human hypophysis was followed by the production of cuboid epithelium lining the thyroid follicles and by diminution in the amount of colloid.

WEIL, Chicago.

Cerebrospinal Fluid

SPONTANEOUS CEREBROSPINAL RHINORRHEA. S. LIVINI, Brit. M. J. **1**:1208 (June 4) 1938.

Livini reports a case of cerebrospinal rhinorrhea in which there was spontaneous recovery. Up to 1934, 66 cases of cerebrospinal rhinorrhea had been reported in the literature. The condition may be associated with hydrocephalus, intracranial tumor or fracture of the skull. In other cases the cause is unknown. One theory attributes spontaneous rhinorrhea to a congenital craniopharyngeal canal, which is forced open by violent coughing or sneezing. Another explanation is that the cerebrospinal fluid tracks down the perineural sheaths of the olfactory nerves. The diagnosis can be established by examination of the fluid which escapes through the nose or by injection of fluorescein into the lumbar subarachnoid space. Cerebrospinal rhinorrhea may cease spontaneously or may require the application of a muscle graft to the olfactory groove. Local applications through the nose are useless and dangerous.

ECHOLS, New Orleans.

OBSERVATIONS ON THE CEREBROSPINAL FLUID PRESSURE ON SIMULTANEOUS VENTRICULAR AND LUMBAR PUNCTURES. G. E. SMYTH and W. R. HENDERSON, J. Neurol. & Psychiat. **1**:226 (July) 1938.

It has been assumed in the past that the ventricular and lumbar cerebrospinal fluid pressures are always in equilibrium except in the presence of spinal block. Smyth and Henderson investigated this relationship in a series of 39 patients. They found in 31 patients, 6 of whom were without gross evidence of intracranial disease and 25 of whom had intracranial tumor, that the lumbar and the ventricular pressures were identical when measured separately, simultaneously, on bilateral jugular compression and after withdrawal of lumbar fluid, irrespective of whether the cerebrospinal fluid pressure was increased. Of the remaining 8 patients, 6 with proved intracranial tumor had a ventricular pressure which was from 20 to 100 mm. higher than the lumbar pressure; this disparity was accentuated by withdrawal of lumbar fluid. In all 8 cases jugular compression revealed a partial block. This difference between the lumbar and the ventricular pressure was associated with a high early operative mortality. In 5 of these cases the tumor was supratentorial, and death was due to herniation of the temporal lobe through the incisura tentorii. Such a disparity between the ventricular and the lumbar pressure may be produced by tentorial herniation through compression of the aqueduct of Sylvius. On the other hand, tonsillar herniation through the foramen magnum produces no difference in pressures. In cases of supratentorial tumors, the ventriculographic procedure and lumbar puncture are especially dangerous, because the disparity in pressure is still further accentuated. Furthermore, tentorial herniation may cause the pontomesencephalic hemorrhages which sometimes occur in cases of supratentorial tumor. These hemorrhages may be attributed to the relative arterial hypertension caused by the inequality of the supratentorial and the subtentorial pressure existing in cases of tentorial herniation.

N. MALAMUD, Ann Arbor, Mich.

Treatment, Neurosurgery

EFFECTIVE USE OF PHENOBARBITAL AND BENZEDRINE SULFATE (AMPHETAMINE SULFATE) IN TREATMENT OF EPILEPSY. B. COHEN and A. MYERSON, Am. J. Psychiat. **95**:371 (Sept.) 1938.

Cohen and Myerson found that use of phenobarbital adjusted individually with reference to the rhythm of each patient's seizures reduced the seizures in male patients by 69 per cent; of the 93 patients treated, 83 were improved. Sixty-seven patients showed a reduction of seizures of 50 per cent or more. Of 50 female patients, 45 were improved, with a total reduction in seizures of 61 per cent. Thirty-four patients showed a reduction in seizures of 50 per cent or more. Benzedrine sulfate proved specific in the treatment of ataxia and drowsiness, which developed in 15 patients in the course of phenobarbital medication. The daily dose of benzedrine sulfate varied from 5 to 20 mg. Use of this drug permits the retention of effective doses of phenobarbital otherwise impossible. It does not increase the number or the severity of epileptic seizures. It has no apparent effect on the sugar, nonprotein nitrogen or creatinine content of the blood or on the basal metabolic rate, pulse rate or blood pressure. There appears to be no necessity for routine catharsis in the treatment of epilepsy when the phenobarbital dosage is adequate.

EDITOR'S ABSTRACT.

SUBARACHNOID ALCOHOL INJECTION FOR RELIEF OF BRACHIAL NEURITIS: USE OF LIPIODAL PRELIMINARY TO HIGH SPINAL ALCOHOL INJECTION. H. C. SALTZSTEIN and F. SCHREIBER, Am. J. Roentgenol. **40**:606 (Oct.) 1938.

Saltzstein and Schreiber think that subarachnoid injection of alcohol for the relief of brachial neuritis is the method of choice for debilitated persons whose life expectancy is uncertain and for whom the safety of major operation is doubtful. The patient is placed on a tilt table. The site of injection is arched with a pillow; the patient is pushed somewhat ventrad, as for spinal injections of alcohol, and the needle is introduced at the desired level. Under roentgenoscopic control, 1 drop of ascending iodized oil is injected. The position of the iodized oil is ascertained. If it is not lying in the region of the roots of the nerve which it is desired to bathe, the table is tilted either up or down until it is exactly in the right place. Two cases are reported to illustrate the usefulness of the injection of iodized oil preliminary to high intraspinal injections of alcohol and to show the consequent relief obtained.

EDITOR'S ABSTRACT.

THE PREVENTION AND TREATMENT OF NEUROSYPHILIS BY COMBINED ARTIFICIAL FEVER AND CHEMOTHERAPY. A. E. BENNETT and MURRAY D. LEWIS, Am. J. Syph., Gonor. & Ven. Dis. **22**:593 (Sept.) 1938.

An early study of the cerebrospinal fluid in patients suffering from syphilis is of the greatest importance, since recognition of the asymptomatic form of neurosyphilis is possible only after a complete study of the cerebrospinal fluid. Fever therapy should be instituted after intensive chemotherapy if the spinal fluid remains resistant or shows progression toward the dementia paralytica type. Reexamination of the spinal fluid is not necessary in cases of latent syphilis after the secondary stage or in those of late syphilis if the spinal fluid findings are completely normal four years after the onset of infection.

After the spirochetes have invaded the systemic tissues, they seem to develop more virulence or to become more heat resistant. For this reason, combined artificial fever and chemotherapy give better clinical and serologic results than either agent alone. In the cases reported artificial fever was induced by means of the Kettering hypertherm. Mapharsen or bismarsen was injected soon after the fever reached its maximum height. Most of the patients received fifty hours of sustained fever at temperatures between 105 and 106 F., usually given in ten weekly sessions of five hours each. Of 10 patients so treated, strongly positive

cerebrospinal findings were completely reversed in 7, partially reversed in 2 and unchanged in 1. Of 19 cases of dementia paralytica, complete remission with full occupational recovery followed in 14, moderate improvement in 3 and no improvement in 2. Of 31 cases of tabes dorsalis of the most severe type complete relief from all symptoms was obtained in 16 cases, or 52 per cent, and improvement in all symptoms, with disappearance of some, in 11 cases, or 35 per cent, while no improvement occurred in only 4, or 13 per cent. Neuritic pains were definitely benefited or relieved in 24 of 28 cases; gastric crises were completely or partially relieved in 11 of 15 cases. Ataxia and urinary incontinence also responded to fever therapy in many of these cases. There was no amelioration in 3 patients with Charcot joints so treated. Of 12 patients with severe disabling types of meningovascular neurosyphilis, 10 obtained complete relief from symptoms; 1 was benefited to some degree, and 1 was not improved. The serologic results did not parallel the clinical improvement. Occasionally the reactions of the spinal fluid of patients only slightly benefited were reversed, while those of patients with definite improvement were not altered.

BECK, Buffalo.

INTRAVENOUS ALDARSONE IN THE TREATMENT OF NEUROSYPHILIS. GORDON R. KAMMAN, Am. J. Syph., Gonor. & Ven. Dis. **22**:638 (Sept.) 1938.

Aldarsone (the formaldehyde sulfoxylate of 3-amino-4-hydroxyl-phenylarsonic acid) is a pentavalent arsenical which contains about 17 per cent of arsenic. It is relatively nontoxic and has been used effectively in the treatment of neurosyphilis. Kamman reports on a series of 53 patients treated with aldarsone. Among them were 35 males and 15 females. The average age was 48 years. There were 4 cases of asymptomatic neurosyphilis, 6 of dementia paralytica of tabetic type, 24 of tabes dorsallis, 17 of early dementia paralytica and 2 of meningovascular neurosyphilis. Forty patients had received previous treatment, with varying results. There was serologic or clinical improvement or both in 69.8 per cent. The condition was unchanged or progressive in 22.7 per cent. In 4 cases of tabes dorsalis the serologic and clinical improvement was accomplished by aldarsone alone. It was unnecessary in any instance to suspend treatment because of changes in the visual fields or optic disks. Toxic reactions were encountered in 3 patients, and in only 1 of these was discontinuance of the drug necessary.

BECK, Buffalo.

THE ADVANTAGES OF LOBECTOMY IN THE TREATMENT OF CEREBRAL GLIOMATA. RUPERT B. RANEY, Bull. Los Angeles Neurol. Soc. **3**:112 (Sept.) 1938.

Raney points out that partial removal of a cerebral glioma fails to accomplish its purpose and may do more harm than good. A carefully performed radical lobectomy causes surprisingly little shock and offers the only hope for a cure. The operative mortality is reduced, and surprisingly few functions may be altered, while many which were lost from the expansion of the tumor may be recovered. Though complete extirpation may be impossible, ample room is obtained to give prolonged relief.

Five cases are reported from a total of 16 in which lobectomy was performed for cerebral tumor. Only 1 of the 16 patients succumbed to the operation, and in this case the patient was already moribund from the effects of an astrocytoma of the left frontal lobe. The patient in the second case also had an astrocytoma of the left frontal lobe, with convulsions and intracranial hypertension. Almost the entire lobe was removed, including part of the motor cortex and Broca's convolution. Operation was followed by thrombosis of the superior longitudinal sinus. Six months later the patient was in good condition, with gradually diminishing aphasia and paralysis of both legs and the right arm. In the third case left frontal lobectomy for glioblastoma multiforme spared the precentral gyrus and Broca's convolution, but extirpation was incomplete, since the tumor extended through the corpus callosum into the right frontal lobe. Death occurred from recurrence

four months after operation, though complete relief from symptoms had been temporarily achieved. The patient in the fourth case was subjected to extensive excision of the right parietal lobe for an astrocytoma. There was complete recovery except for left hemiparesis, hemianesthesia and hemianopia; the patient walked from the hospital on the thirteenth day after the operation. Four months after this operation he was still improving. In the fifth case a patient with glioblastoma multiforme in the right temporal lobe was almost completely relieved by lobectomy of moria, auditory and visual hallucinations, memory defect and confusion, and four months after the operation he was again managing his vegetable market.

Raney concludes that all "malignant" tumors should be removed by lobectomy until a more successful treatment is devised. Since "benign" tumors cannot be differentiated before operation, in no case should operation be abandoned. By the use of lobectomy months of normal rather than of vegetative existence are added to the patient's life. Serious complications may occur, but these are of less importance than those which result when a tumor is left to continue its growth.

MACKAY, Chicago.

THE TREATMENT OF A CRETIN WITH ANTERIOR PITUITARY EXTRACT. G. DE M. RUDOLPH, Endocrinology **23**:364 (Sept.) 1938.

The author reports the results of five and one-half years of intermittent treatment of a cretin boy. Improvement from the age of 18 months with doses of ¼ grain (0.016 Gm.) of thyroid was interrupted by an operation for mastoiditis. After this operation the administration of thyroid produced drowsiness and lethargy. A pituitary extract containing the growth hormone (antuitrin-G) given in doses of 10 rat units every two weeks proved helpful. The dose was increased to 20 rat units once a week, and improvement in both the physical and the mental sphere was accelerated. The study was terminated at the age of 7 by death from pneumonia.

PALMER, Philadelphia.

TREATMENT OF EPILEPSY WITH SYNERGISTIC COMBINATION OF PHENOBARBITAL AND BELLADONNA. A. E. LOSCALZO, J. Nerv. & Ment. Dis. **88**:500 (Oct.) 1938.

Loscalzo compared the effect of phenobarbital plus a mixture of potassium bromide and chloral hydrate and that of phenobarbital plus levorotatory belladonna alkaloids in 32 cases of epilepsy (idiopathic) of unknown cause. The patients were under observation for one year or more. During the first twenty-six weeks the patients were given from ¼ to ½ grain (0.016 to 0.032 Gm.) of phenobarbital three times a day, and more than half the group received in addition daily doses of a mixture of 7½ grains (0.5 Gm.) of potassium bromide and 7½ grains of chloral hydrate. The dosage of phenobarbital was arbitrarily established, although attempts were made to adjust the quantity to the requirement of the individual patient. The number of seizures experienced was 804. An almost universal complaint was that the medication produced a state of lethargy and at times somnolence. During the second period of twenty-six weeks, as a test of the observations of Friedberg, the 32 patients were given tablets containing ¼ grain (0.05 Gm.) of phenobarbital and $\frac{1}{250}$ grain (0.00026 Gm.) of levorotatory belladonna alkaloids. The dose was usually ½ tablet three times a day for those with less severe and less frequent seizures, ½ tablet four times a day for those with the moderately severe and more frequent type and 1 tablet three times a day for those whose condition necessitated the greatest degree of sedation. No other medication was employed. A total of 612 seizures occurred. There were no complaints of lethargy or somnolence except by the few patients who ingested the largest doses. About 40 per cent of these patients also stated that their convulsions now were much less severe. The patients were unaware of any change in medication, except that those who had previously taken both phenobarbital and the solution of bromide and chloral hydrate knew that the liquid had been discontinued. Consequently, any possible psychic effect was largely obviated. For the majority of patients the

reduction in the number of seizures corresponded closely to the average result of slightly less than 24 per cent. Individual variations in response to the drug in a few patients, however, resulted in a decrease of from 50 to 60 per cent in the number of attacks, while in a limited number of less responsive patients a reduction of only from 5 to 10 per cent was noted. While there was a notable reduction in grand mal seizures, there was no alteration in the number of petit mal attacks.

EDITOR'S ABSTRACT.

TREATMENT OF MENINGOCOCCIC MENINGITIS: INTRASPINAL USE OF ANTIMENINGOCOCCUS SERUM AT BELLEVUE HOSPITAL, 1928 TO 1936. N. W. BOLDUAN, J. Pediat. **13**:357 (Sept.) 1938.

Bolduan records the results of the intraspinal use of antimeningococcus serum in 191 patients ranging in age from infancy to 12 years. During the years 1928 to 1932 the majority of the patients received serum intraspinally once every twenty-four hours, while from 1932 to 1936 serum was given intraspinally every twelve hours until definite improvement ensued. The criteria for discontinuing serum therapy were decrease of pleocytosis to a count of about 500 cells or less, normal or rapidly falling leukocytosis, increasing sugar in the spinal fluid and persistently negative spinal fluid cultures. If the aforementioned criteria had not been attained after four or five days, a change in the type of serum was made, often with beneficial outcome. There were 48 deaths. This included 1 patient who died of secondary streptococcic meningitis and 18 patients who received no treatment (postmortem diagnosis) or died within twelve hours of the initiation of therapy. Complications (arthritis, otitis media, mastoiditis, nerve deafness, ophthalmitis and blindness) developed in from 35 to 40 per cent of the patients. In 1928 and 1929 about 155 cc. of serum was used per patient, and in 1935 and 1936 the average was 165 cc. Of 48 patients who between 1928 and 1936 received serum by the intravenous as well as by the intraspinal route (usually from 20 to 30 cc. intravenously), 10 died. In the group who did not receive serum intravenously there were 38 deaths among 143 patients. The rate for 1935 and 1936 of but 3 deaths among 46 patients (7 per cent) as compared with 22 deaths among 94 patients (23 per cent) is ample confirmation of the author's faith in the orthodox method of therapy. During 1928 and 1929, of 80 patients who survived one week, 68 stayed in the hospital longer than two weeks. In 1935 and 1936, of 43 patients who survived one week, only 25 stayed longer than two weeks. In seeking a cause for the reduction in the fatality rate and in the period of hospitalization from 1928 through 1936, it was thought at first that the administration of serum at intervals of twelve hours was largely responsible. However, two other possibilities had to be considered: a change in the virulence of the organism and an increase in the potency of the serum used. However, from figures obtained from the New York City Department of Health, the organisms responsible for the 1935-1936 outbreak were quite as virulent as those in 1928 and 1929. Therefore, a part of the reduction in the fatality rate must be ascribed to an increase in the potency of the serums used. Nevertheless, the interval between doses contributed in part to the reduction in mortality.

EDITOR'S ABSTRACT.

SURGICAL TREATMENT OF EPILEPSY. J. P. EVANS, Ohio State M. J. **34**:1229 (Nov.) 1938.

Evans states that the first requirement in selecting cases of epilepsy for surgical intervention is that the epilepsy be due to focal lesions in the brain. It might then appear that any generalized seizure would be excluded from consideration at the outset. This, however, is not always so, for it is conceivable that a seizure firing, for example, from one of the frontal poles, might work up its abnormal cerebral rhythm in a silent area of the brain and that the seizure would then spread rapidly, firing off the entire body musculature at one time. It is the usual rule, however, that generalized seizures less often prove susceptible to surgical intervention. It

is essential to analyze carefully both the subjective and the objective course of events in the patient's seizure and thus sort out by detailed analysis signs which indicate the initial area of abnormal discharge. Another criterion for the selection of cases in which surgical intervention is suitable is the pneumoencephalographic evidence of focal damage. A third criterion is the finding at the site of suspected pathologic change variations of electrical potential characteristic of epileptic discharge. Use of this method depends on further elaboration of the methods of electroencephalography. However, before radical excision of the suspected area is undertaken a fourth criterion should be met—the production of a characteristic seizure by carefully controlled electrical stimulation of the exposed cortex. Finally, any patient should have, before operation is seriously considered, a thorough trial of phenobarbital or other sedative therapy, partly to avoid unnecessary operation and partly to prove that any postoperative sedation employed is not the cause of postoperative improvement rather than the operation itself. The aim of operative intervention is to excise the damaged area of the brain, leaving a lesser degree of damage than was caused by the original injury. This involves an understanding of the anatomic arrangement of the blood vessels and of the physiologic factors in collateral circulation. The author concludes that the results of radical excision of cerebral cicatrix are, in his opinion, such as to justify further intelligent and critical pursuit of the problem.

J. A. M. A.

USE OF INTRAVENOUS SODIUM AMYTAL IN PSYCHOGENIC AMNESIC STATES. M. HERMAN, Psychiatric Quart. **12**:738 (Oct.) 1938.

Herman restored the memory of 6 persons with hysterical amnesia by intravenous use of sodium amytal. Memory was restored within a few minutes. In each case other methods, including hypnosis, had been tried without success. Many theories have been evoked to explain the action of sodium amytal in producing its psychologic effect. The most likely theory is the physiologic explanation that sodium amytal is a cortical depressant and tends to diminish the normal inhibitory action of the cortical cells.

EDITOR'S ABSTRACT.

ROLE OF HYPERTONIC SOLUTIONS IN TREATMENT OF MIGRAINE. G. VILLEY, J. F. BUVAT and BUVAT-POCHON, Rev. neurol. **70**:32 (July) 1938.

Villey and the Buvats report the results they obtained with the intravenous injection of hypertonic solutions of sodium chloride in the course of attacks of migraine. They present a detailed clinical history which suggested to them that the disturbances presented by this patient were related to a paroxysmal attack of intracranial hypertension. Accordingly, they subjected the patient to intravenous injections of hypertonic solution of sodium chloride from the beginning of the painful period of his attack. The pain ceased during the first hour after the injection; the subconfusional condition disappeared within several hours. The authors treated the patient in this manner for a year; at each treatment the pain subsided in from twenty to forty minutes; the effect on the state of confusion varied. They cite the clinical histories of several other patients who had migraine of a more typical character. The histories indicate that 20 cc. was the dose usually administered by intravenous injection; the concentration of the solution was either 10 or 20 per cent.

EDITOR'S ABSTRACT.

Society Transactions

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MORRIS GROSSMAN, M.D., *Chairman, Presiding*

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PATHOLOGIC ASPECTS OF SOME FORMS OF TRAUMA TO THE BRAIN AND SPINAL CORD. DR. LEWIS D. STEVENSON.

Only a few aspects of trauma to the nervous system are presented. The history of fractures of the skull and neck dates back to the building of the pyramids, but the problem has become serious only since the advent of the motor car and the drunken driver. Not only the number of persons who are killed or injured and require treatment but the medicolegal problem is serious. One of the most amazing aspects is malingering, even in cases of negligible trauma. The value of encephalograms in distinguishing between localized trauma and diffuse vascular disease should be noted. Trauma to the nervous system often is seen at birth, and the various accidents to the brain and brachial plexus during labor are well known. Injuries to the cord, however, are not sufficiently emphasized.

Twenty-one cases of various forms of trauma, illustrated with lantern slides, are presented. There are 7 cases of injury to the cord, in 1 of which there was trauma at birth, with hematomyelia and hemorrhage into the medulla; in the other 6 injury to the cord occurred in the adult. In 1 of these cases there was fracture dislocation of the neck, causing extensive damage in the cord with signs of complete transverse lesion, and in another, fracture dislocation through the fourth cervical vertebra with hemorrhage into the spinal cord. In another, a woman fell from a subway platform, striking the back of her head and neck. She did not lose consciousness, but immediately after the fall was aware that she could not move either leg; then she noticed difficulty in moving hands; there was almost complete softening of the spinal cord, without fracture or dislocation of the spine or any evidence of hemorrhage in the cord. In another case of fracture dislocation of the neck, sustained in a diving accident, there was some damage to the spinal cord. Other types of injury are gunshot and stab wounds of the spinal cord, with degeneration in the cord.

Several illustrations of intracranial injury are presented. The first case is one of bilateral epidural hemorrhage. Epidural hemorrhage is usually unilateral and results from a fracture of the skull crossing one of the branches of the middle meningeal artery. Such a hemorrhage, however, may be due to venous bleeding and may sometimes occur without fracture of the skull. Necropsy showed this condition to be the cause of death in 61 of a series of cases of fracture of the skull reported by the medical examiner. The next case is one of severe injury to the head in which there was bleeding into the subdural and subarachnoid spaces, with severe laceration of the brain; the next is a case of subdural hematoma with a notch in the peduncle on one side. The subdural hematoma was in the right frontoparietal region, with considerable distortion and compression of the right hemisphere, displacement of the ventricles beyond the midline and an incisura in the left cerebral peduncle. The patient had weakness of both upper extremities, and weakness of the right leg was greater than that of the left, showing a greater loss of strength on the side of the hematoma.

The mechanism of ipsilateral hemiplegia in cases of subdural hematoma is described, with notching of the peduncle on the side opposite the lesion in the

brain; the notch in the present case evidently was caused by pressure of the brain stem against the free margin of the tentorium of the cerebellum, thus bringing the paralysis back to the side of the lesion. In chronic subdural hematoma there is development of a membrane. This type of hematoma may cause few or no symptoms for a considerable period following the trauma. The lesion, according to Gardner, enlarges by accumulation of fluid in the sac which is formed about the subdural hemorrhage. These lesions are frequently found without fracture of the skull and usually result from tear of a cerebral vein. They are said to be common in cases of trauma to the front or back of the head. Then there is a case of meningitis associated with fracture of the skull, which is of interest only in that the organism was the meningococcus.

The next few cases are those of accidental postoperative death, in which there were: trauma to the brain (with large hemorrhage) resulting from needle punctures; hemorrhage into the brain resulting from operative intervention in a case of jacksonian epilepsy in which the pacchionian granulations were loosened; interference with the blood supply caused by manipulation of the cord during chordotomy, and subarachnoid hemorrhage resulting from cisternal puncture and extending the entire length of the cord.

The next case is one of caisson disease with destruction of the substance of the cord, produced by the release of nitrogen bubbles during too rapid decompression in the case of a man working in compressed air.

DISCUSSION

DR. BENJAMIN M. VANCE: Those of us in the medical examiner's office who have worked at the city morgue have known Dr. Stevenson for a number of years, and we have brought many cases of difficult diagnosis to him for assistance and advice. He has always been helpful. I am glad that he has presented the subject in the way he has, for the neuropathologic conditions produced by trauma have not received their due recognition until recent years. Dr. Stevenson has spoken of the results of trauma due to violence acting directly on the brain and spinal cord. He has not discussed the indirect action of trauma on the central nervous system, especially trauma to some other part of the body, which produces its effects by some form of embolism.

I shall say a few words about the effects of fat embolism on the human body, especially on the central nervous system. I shall disregard all forms of fat embolism except those produced by fracture of the long bones. With this injury there is destruction of many fat cells in the vicinity of the fracture, with tearing of some of the smaller veins in the bone marrow and surrounding tissues. In a few cases enough fat is forced into the veins and carried into the pulmonary circulation to cause clinical symptoms.

The clinical effects of fat embolism are classified under two categories: first, pulmonary fat embolism, which produces obstruction to the pulmonary circulation and may cause death by asphyxia, and, second, cerebral fat embolism, which occurs when the fat is forced through the pulmonary circulation into the systemic arterial circulation, by which it is carried to all the organs of the body—the skin, the heart, the kidneys and, most important, the brain. In the cerebral type of fat embolism the symptoms are caused by the action of the emboli on the central nervous system. In most cases, about sixteen to thirty-two hours after the fracture the patient gradually sinks into coma, and at the same time there develop a large number of petechial hemorrhages, especially on the shoulders, neck and upper part of the chest, which have the peculiarity of being grouped in small colonies. The coma deepens until the patient dies. It is not attended necessarily by a rise in blood pressure or any distinctive neurologic signs. Death usually occurs from thirty-two hours to seven days later. At autopsy the chief lesion is a large number of petechial hemorrhages in the brain, which I can demonstrate best by the lantern slides. Slide 1 shows a microscopic section of the lung of a patient with pulmonary fat embolism who died of asphyxia. The fat fills all the capillaries. In some cases the fat in the capillaries may be forced into the systemic circulation. Slide 2

shows the brain in a case of cerebral fat embolism, with multiple petechial hemorrhages in the white matter, grouped in small colonies of from four to twelve. These hemorrhages are rarely seen in the gray matter. Slide 3 is a picture of a similar brain in another case of cerebral fat embolism. Slide 4 shows a section of the brain in a case of cerebral fat embolism which is stained with osmic acid. Two distinct lesions are noted: (1) the ring hemorrhage, characterized by a fat embolus in a small arteriole which is surrounded by a necrotic zone of brain tissue and, in turn, is ringed by a zone of red blood cells; (2) an area of rarefaction, which I shall demonstrate later. Slide 5 indicates the differences between a brain showing the petechial hemorrhages of fat embolism and a brain showing concussion hemorrhages, due to trauma applied to the head. The concussion hemorrhages are caused by jarring of the skull and rupture of some of the minute blood vessels in the brain. The latter vary in size and are not grouped characteristically in colonies. In microscopic sections no fat emboli are to be seen in blood vessels associated with these hemorrhages. Slide 6 shows a ring hemorrhage at the bifurcation of a vessel. Slide 7 shows the lesion called an area of rarefaction, which is caused by fat emboli blocking a group of small blood vessels, so that the central area surrounded by these vessels undergoes degeneration, loses all its myelin and becomes a minute translucent area in the brain tissue. The obstruction of the vessels prevents hemorrhage around the necrotic area.

It is my opinion that both the ring hemorrhages and the areas of rarefaction are microscopic infarcts which occur as the result of emboli in the small arteries of the brain. They are present in huge numbers in cases of cerebral fat embolism and produce the characteristic symptoms. The clinical importance of this condition is that in some cases both the skull and a long bone in one of the lower extremities may be fractured, so that if the patient sinks into coma it may be a difficult diagnostic problem to ascertain whether the signs are produced by an intracranial hemorrhage, such as an epidural hemorrhage which might be amenable to surgical intervention, or cerebral fat embolism, which would not be benefited by a craniotomy.

Dr. Milton Helpern: Dr. Stevenson has invited me to discuss his paper with particular reference to an unusual case in which I performed autopsy in the office of the chief medical examiner and which illustrates an indirect effect of trauma on the brain. This case may be one of air embolism, although I am not certain as to how great a role the air embolism played in producing the lesion in the brain. At any rate, the lesion encountered in the brain resulted from a traumatic injury elsewhere in the body.

In this case, a man aged 35 was stabbed several times in the chest. He was admitted to the Roosevelt Hospital, where it was found that one wound passed through the lower part of the sternum and another through the left side of the chest. He was conscious, but it was noted shortly after admission that he was cyanotic, the cyanosis involving first the face and then the neck and spreading gradually to the chest and upper part of the abdomen. He remained in this state for about two days; on the third day he suddenly became comatose and died. No operation was performed. Autopsy showed a small stab wound, penetrating the sternum, pericardium and right ventricle of the heart. The wound in the heart had been sealed off spontaneously by the formation of a thrombus, so that no blood was seen in the pericardial sac. The second wound penetrated the left side of the chest, entering the substance of the left lung about ½ inch (1.27 cm.). The surface wound sealed itself off, and the lung remained in an expanded position. The wound involved a tributary of the pulmonary vein and one of the smaller bronchi, establishing a fistulous connection between them. At the time of autopsy no thrombi were seen in the heart or superior vena cava; the jugular and innominate veins were much dilated, but contained only fluid blood and soft postmortem clots.

A remarkable lesion was seen in the brain. The surface appeared congested, and on section a great many punctate and larger hemorrhages were seen dis-

tributed throughout the entire white matter, including the corpus callosum. Some of these hemorrhages were conglomerate. They were also observed in the pons and cerebellum.

Examination of frozen sections stained with sudan III revealed no fat in the vessels. Microscopic examination showed that the small hemorrhages were of the ring type, but there were also larger, more irregularly shaped hemorrhages, of the so-called ball type. In the areas of the hemorrhages the capillary blood vessels contained many small bubbles, separating and displacing the red cells. There was no inflammatory reaction in these areas. Fat embolism was definitely ruled out. The idea presented itself that the bubbles might be air which had passed into the systemic circulation and thus into the brain from the bronchovenous fistula in the lung. I believe that the stasis of blood in the superior vena cava which was caused by the stab wound in the right ventricle was an important, but not the only, factor in the causation of the hemorrhages in the brain. The cerebral hemorrhages in this case probably resulted from the rare fortuitous combination of a not immediately fatal stab wound of the right cardiac ventricle, causing systemic venous stasis, and another stab wound of the lung, causing systemic air embolism through a bronchovenous fistula. I have never encountered a lesion such as was seen in this brain in cases of isolated stab wounds of the right ventricle in which the patients survived for a period after suturing or in cases of isolated stab wounds of the lung.

DR. RICHARD M. BRICKNER: Can Dr. Stevenson say more about the accessory hemorrhages he has seen in cases of subdural hematoma, particularly with reference to the growth of the masses as a whole?

DR. LEWIS D. STEVENSON: In answer to Dr. Brickner, I can only show these colored photomicrographs of a subdural hematoma. They illustrate two mechanisms that have increased the size of the lesion in the skull. The blood cells, too, seem to be well preserved—they are not broken up—and there is not much fluid inside the sac; I do not think this case contributes much to the theory of osmosis as the cause of the increase in size of chronic subdural hematoma.

ROENTGENOLOGIC ASPECTS OF FRACTURES OF THE SKULL AND INJURIES TO THE BRAIN. DR. CORNELIUS G. DYKE.

The various types of fractures of the vault and of the base are reviewed. Comments are made on the appearance of recent and old fractures and the time necessary for fractures to heal. The limitations of the roentgen diagnosis of fractures of the skull, particularly those affecting the base, are discussed.

With regard to the roentgenologic aspects of injuries to the brain, such lesions as porencephaly, unilateral and bilateral cerebral atrophy, as evidenced by dilatation of part or all of one or both lateral ventricles, and cerebral sulci are discussed and demonstrated with lantern slides. Several cases of cerebral hemiatrophy with homolateral hypertrophy of the skull and sinuses are described. It is emphasized that in some of the cases the condition is progressive, as indicated in the encephalograms by increasing enlargements of one of the lateral ventricles. The problem of the diagnosis of chronic subdural hematoma is presented from the roentgenologic point of view. It is emphasized that in infants diagnosis from the roentgenogram is often impossible, even when an air study is performed. In several cases of calcified chronic subdural hematomas the changes, such as thickening of the skull, hypertrophy of the sinuses and atrophy of the brain, as indicated by enlargement of the lateral ventricle on the side of the hematoma, are described. Finally, the usual pneumoencephalographic evidences of the ordinary type of chronic subdural hematoma are enumerated.

DISCUSSION

DR. LEO M. DAVIDOFF: The discussion of a paper by Dr. Dyke on the roentgen diagnosis of any condition of the skull and its contents is analogous to the useless practice of gilding a lily. If Dr. Dyke has made any omissions in his paper it is

due to the vastness of the subject, which it would be impossible to cover even in a much longer period. Since subdural hematoma is an important subdivision of trauma to the central nervous system, I wish to call attention to a condition which, though rare, is of considerable interest because it shows some of the mechanisms of the formation and behavior of subdural hematomas in the cranial cavity. Four cases which Dr. Dyke and I studied are described.

A girl aged about 16 was admitted to the Neurological Institute of New York with a history of having injured her head by falling down stairs four months previous to admission. Headache developed; examination showed asymmetry of the face, greater prominence of the right eye, palsy of the right sixth nerve and slight increase of reflexes on the left side. In the presence of this asymmetry, it seemed that the trauma might be incidental to her condition, and it was more or less disregarded. Roentgenograms of the skull showed some changes, leading to a suspicion of congenital tumor in the right frontal region. Since this evidence was not sufficient, an encephalogram was made, which tended to confirm the presence of a mass in the frontal region. At operation a large subdural hematoma was seen. It was unusual in that the membrane was fibrosed and thick, but the contents of the sac consisted of a great deal of brownish liquid, in addition to a fibrotic clot.

An encephalogram (lantern slide) showed bulging of the temporal region, slight displacement of the ventricular system, slight enlargement of the ethmoid sinuses and projection outward of the supraorbital region on the right side. It showed also disappearance of the oblique line which marks the anterior edge of the temporal bone, which is seen clearly on the slide.

Consideration suggested that the history of trauma, four months previous to the onset of symptoms, could not account for the marked changes in the skull. Further history revealed that at the age of 5 the child had had an equally severe trauma, on falling down a flight of stone steps. After this accident she had been unconscious and in a hospital for three or four weeks, with eventual recovery. It seemed that this injury, at the age of 5, might have caused a hematoma, which had been partly absorbed or become stationary and had left the child without symptoms until a second injury, which led to further bleeding into the sac of the hematoma.

After this case it was possible to demonstrate similar lesions and changes in the skull in 4 other cases.

In a second case, a youth aged about 18, had a history of hematoma, ostensibly of only a few months' duration, following trauma during boxing. In the encephalogram there are the charactseristic slight displacement of the ventricle and dilatation of the sinus and, in this case, thickening of the bone with thinning in the temporal region. The similarity of some of these changes to those which Dr. Dyke described as resulting from injury in childhood in the case of unilateral atrophy of the hemisphere is evident. My theory is that a subdural hematoma occurs at the time of the original injury, followed by absorption of the contents, which results in shrinkage of the brain on that side. The reaction is the same as that in cases of atrophy of the brain without hemorrhage, dilatation of the sinuses or thickening of the vault, as Dr. Dyke described. When there is relighting of the process by a further injury, pressure symptoms return. The reason why there is so little displacement seems to be that the cranial cavity has room to spare, so that when there is an increase in the size of the hematoma the ventricle is not displayed as much as it would be in an adult suffering from hematoma for the first time.

In a third case a young man had had a boxing injury similar to that in the previous case. In a review of his past history it was found that he had fallen out of a tree, fractured his leg and been laid up in a hospital for six months. The injury was associated with a period of unconsciousness—probably a cerebral injury with subdural hematoma. In the encephalogram there are marked elevation of the orbital plate on the side of the lesion, some increase in ethmoid cells and other changes, which are not obvious in the lateral view.

The fourth lantern slide is an encephalogram taken in the same case, showing the changes to which I called attention—enlargement of the orbital plate, thickening of the skull, even slight elevation of the petrous bone on that side, with slight shifting of the ventricular system away from the lesion.

DR. EMANUEL D. FRIEDMAN: I shall not make any comment on Dr. Dyke's interpretations of routine roentgenograms of the skull, but shall take the liberty of commenting on the subject of encephalographic changes following injuries to the skull. The literature, abroad and in America, is full of references to such changes. I think most would concede that in the interpretation of aerograms in cases of trauma, importance attaches chiefly to unilateral changes. These were described long ago by Foerster, Schwab and others as enlargement of the ventricular system on the side of the injury, with migration of the ventricle toward the surface; this is seen particularly in cases in which the injury is followed by post-traumatic epilepsy, for relief of which Foerster and Penfield have suggested the operation of excision of the cerebral scar. However, I do not think I should be as ready to negate the significance of diffuse enlargement of the ventricular system following injury to the skull, particularly when the injury has been severe. The exact pathologic changes are not known, but there are a number of theories as to the reason for the changes following trauma. There are the traumatic encephalitis of Osnato and the observations by Beling and Martland. Marburg expressed the opinion that there is actual damage to the vessels following trauma, and on this basis German authors attempted to explain the late sequelae of trauma. Bollinger explained the late apoplexy following trauma in this way.

It may be that in Dr. Stevenson's case, which he called one of concussion of the spine, the changes were dependent on traumatic damage to the vessels and the subsequent formation of ischemic cysts in the cord.

On the basis of these theories and the work of Ricker on local vasomotor palsies and that of Spielmeyer on ischemic necrobiosis following damage to vessels, one might postulate that in a certain percentage of cases of injury to the skull there are factors, from whatever cause, which lead to changes in the central nervous system and diffuse internal hydrocephalus.

I do not mean that an encephalogram alone makes a possible diagnosis. It is simply an adjuvant in coming to a decision, and I believe it has its place in the evaluation of the after-effects of injuries to the skull.

A number of years ago, in a study in which Drs. Stevenson, Wortis, Kennedy and I took part, we reported about 20 cases, from the neurologic service of Bellevue Hospital, of injuries to the skull, with encephalographic changes. In 19 of the 20 cases studied we found changes which we thought justified the assumption of damage to the brain. I believe, therefore that in every case in which a patient complains persistently of symptoms and the injury is bona fide and severe it is the duty of the diagnostician to make use of every means at his command to exclude organic disease. It is only in this way that I should interpret the value of the encephalogram.

DR. LEWIS D. STEVENSON: May I ask Dr. Dyke and Dr. Davidoff a question? I have attempted this evening to show that there may be loss of substance in the spinal cord from concussion. It has been demonstrated before that the same effect may arise from commotion of the brain substance. Is there any evidence in the cases recently reported that the young patients actually had subdural hematomas and that they eventually had a second trauma with a second hematoma? Could the matter not be explained on the basis of injury to the brain with loss of substance and one hematoma?

DR. LEON HASTINGS CORNWALL: Like the paper by Dr. Stevenson, Dr. Dyke's contribution has been interesting, instructive and illuminating. One must recognize speculation for what it is. All have to conjecture at times when they seek to clarify obscurities, but I wish to express a view in accordance with what Dr. Stevenson has said. I cannot accept, without certain mental reservations, the conclusion in the cases of atrophy or hypoplasia of the brain, ipsilateral hypertrophy

of the calvarium and alteration of the sinuses. Anomalies of the sinuses are common in persons who have no disease. The fact that the sinuses were enlarged on the same side as the cerebral hypoplasia and hypertrophy of the skull, in conjunction with antecedent subdural hematoma—if the last can be established beyond question—supports, but I do not think proves, the explanation that has been given.

There is one other statement that I wish to challenge, though not too severely—it is that calcification in cases of cerebral hemorrhage is rare. If Dr. Dyke means that the roentgenologic discovery of calcification in such cases is rare I cannot disagree with him, but I cannot accept the general statement that calcification in all hemorrhages of the brain is rare because in hemorrhages elsewhere in the body it is certainly not infrequent.

Before Drs. Martland and Beling presented the paper (Traumatic Cerebral Hemorrhage, ARCH. NEUROL. & PSYCHIAT. **22**:1001 [Nov.] 1929) before the American Neurological Association to which reference has been made this evening, and three years after Dr. Cassasa read his paper (Multiple Traumatic Cerebral Hemorrhages, *Proc. New York Path. Soc.* **24**:101, 1924), Drs. Michael Osnato and Vincent Giliberti published a paper entitled "Postconcussion Neurosis—Traumatic Encephalitis" (ARCH. NEUROL. & PSYCHIAT. **18**:181 [Aug.] 1927). At that time Dr. Cassasa was a deputy medical examiner; he gave Dr. Osnato the brain of a man who died about thirty-six hours after an injury to the head which was not accompanied by any fracture of the bones. I studied the brain, and the observations constitute a part of the paper by Drs. Osnato and Giliberti. Many of the lesions of which Dr. Vance has spoken were encountered. Among others, there were extensive fat emboli similar to those that Dr. Vance has shown. A point that intrigued me at the time, and still interests and perplexes me, is the mechanism by which the fat emboli were formed. If there were no fractures I can only speculate concerning the matter. A physical chemist doubtless could throw light on the mechanism concerned by relating it to a change in the colloidal state of the blood, as the result of commotion resulting in an alteration of the normal dispersion of fat globules. I wonder if Dr. Vance has encountered similar cases? He may recall the patient of whom I have spoken. At the time when this observation was recorded, some pathologists looked askance on fat embolism and were inclined to ridicule the idea that it ever did much harm, although it had been recorded in the literature for many years.

DR. CORNELIUS G. DYKE: With regard to Dr. Stevenson's question about his patient with relapsing juvenile chronic subdural hematoma on the left side: I questioned the patient's mother as to whether he ever had received any serious injury to the head in childhood. She told me that he had been struck in the left temporal region by a baseball at the age of 9. This resulted in a laceration of the scalp which required surgical attention. The other patients with relapsing juvenile chronic subdural hematoma gave definite histories of repeated injuries to the head.

As to Dr. Cornwall's question pertaining to calcification in the brain, if I understood him correctly: I did not say that calcification in the brain is infrequent. I did say that the number of reported cases of calcified subdural hematoma is small. There are only half a dozen or so verified cases in the literature.

The other question by Dr. Cornwall concerning his doubt that cerebral atrophy has any relation to ipsilateral hypertrophy of bone and sinuses I can best answer by extending to him an invitation to visit me. I will show him so many cases of hemiatrophy of the brain with homolateral hypertrophy of the skull and sinuses that I believe he will be in no doubt about the relation between them.

In regard to the question relating to the proof of the existence of relapsing juvenile chronic subdural hematoma in the cases which Dr. Davidoff and I studied: It is hard to prove anything, but there seemed to be a definite connection between the old injuries which the patients suffered and the changes in the bones and sinuses that Dr. Davidoff discussed. The changes in the bones are the effects of initial localized increased intracranial pressure, resulting in expan-

sion of a middle fossa. They are: the squamous portion of the temporal bone is displaced laterally; the greater wing of the sphenoid bone is pushed downward and forward, and the lesser wing of the sphenoid bone is pushed upward.

Besides the evidence of localized increased intracranial pressure, there are also changes in the skull indicating localized diminished pressure. These are: thickening of the bone and hypertrophy of the paranasal sinuses adjacent to the hematoma. It is possible that such changes in the bone and sinuses may be coincidental, but when they occur repeatedly I think it is justifiable to consider them of some significance. The last thing that happens after the phase of negative pressure is an increase in the intracranial pressure, due to "lighting up" of the hematoma by the more recent injury, which brings the patient to the hospital with signs of an expanding intracranial lesion. It has not been proved that this condition forms a definite entity, but the evidence offered is suggestive.

A Comparative Study of the Dehydrating Action of Dextrose, Sucrose, Sodium Chloride, Sorbitol and Caffeine as Determined by Changes in the Cerebrospinal Fluid Pressure. Drs. E. Jefferson Browder and Floyd H. Bragdon, Brooklyn.

This preliminary report is concerned with an analysis of the detailed observations made in 38 experiments on the human subject relative to the changes in blood pressure, pulse rate, respiratory rate and cerebrospinal fluid pressure following the administration of chemicals designed to reduce intracranial tension. The solutions used were 50 per cent dextrose, in 100 cc. doses; 50 per cent sucrose, in 100 cc. doses; 10 per cent sodium chloride, in 100 cc. doses; 50 per cent sorbitol, in 50 cc. doses, and caffeine with sodium benzoate, 0.5 Gm. hourly for three hours. The experimental subjects selected were patients with tumor of the brain, recent trauma to the brain and spontaneous intracerebral hemorrhage.

Each experiment was conducted with the patient in a lateral horizontal position, with a sphygmomanometer attached to the upper part of the arm and with a 17 gage lumbar puncture needle, attached to a mercury spinal manometer, introduced into the lumbar thecal sac, without external loss of cerebrospinal fluid. As a control in each instance, the blood pressure, pulse rate, respiratory rate and cerebrospinal fluid pressure were recorded every five minutes throughout periods varying from twenty to forty minutes. After the establishment of a "control level," the solution to be used was injected either intravenously (sugars and salts) or intramuscularly (caffeine). Records of the blood pressure, pulse rate, respiratory rate and cerebrospinal fluid pressure were continued every ten minutes for variable periods ranging from one hour and thirty minutes to six hours. No noteworthy changes in blood pressure, pulse rate or respiratory rate were observed in any of the experiments; consequently, these will not be discussed in this paper.

As controls, 8 of the experiments were carried out on patients who showed no clinical evidence of disease of the central nervous system. In 2 cases each dextrose, sucrose or sorbitol were administered intravenously; in 1 instance sodium chloride, and in another caffeine with sodium benzoate, was given intramuscularly in 0.5 Gm. quantities hourly for three hours. In 6 of these 8 experiments a reduction in cerebrospinal fluid pressure was effected, which persisted for an average period of three hours, all five of the dehydrating agents being represented; in the remaining 2 cases no appreciable alteration in the cerebrospinal fluid pressure was noted after the intravenous injection of sucrose and sodium chloride, respectively. No secondary rise was observed after the initial reduction in cerebrospinal fluid pressure in any of the experiments with the normal group, and the longest period of reduction of pressure occurred after one injection of dextrose.

Six detailed observations were made on patients with recent trauma to the brain, dextrose, sucrose and sorbitol being used as the dehydrating agent in 2 instances each. The solution of dextrose administered intravenously produced the expected reduction in cerebrospinal fluid pressure in one instance and a progressive rise in the other. The injection of sucrose effected a reduction in cerebro-

spinal fluid pressure in both cases; however, in 1 of these there occurred a secondary rise in pressure at the end of two hours after the injection, which reached a level considerably above that recorded during the control period. The results following the administration of sorbitol were similar to the observations made after the injection of dextrose: namely, in 1 instance a reduction in pressure, and in the other a slow, progressive rise in the cerebrospinal fluid pressure, beginning at the period of injection.

Twelve experiments were carried out before operation on patients with verified tumors of the brain. A solution of dextrose was used in 3 experiments; in each case prompt reduction in cerebrospinal fluid pressure was effected; however, in no instance was this reduction maintained for longer than one hour, and in all 3 instances there was a secondary rise in pressure. Sorbitol was used in 4 cases, and in each experiment there was a prompt reduction in cerebrospinal fluid pressure, which held for an average of forty-five minutes, but was followed by a secondary rise in pressure in each instance, to a level well above that recorded before the injection. A solution of sucrose was used in 3 experiments. In 2 of these there was a recorded reduction in cerebrospinal fluid pressure lasting approximately one and one-half hours each, with no secondary rise in pressure, whereas in the third experiment a reduction in pressure was produced, followed, however, in one hour and fifteen minutes by a marked secondary rise in pressure. One prolonged study was made concerning the effect of caffeine. After the first hourly intramuscular injection of 0.5 Gm. of caffeine with sodium benzoate the cerebrospinal fluid pressure showed only a moderate reduction, and this was maintained for only thirty minutes. Sodium chloride was used in this group of the patients only once; a marked reduction of cerebrospinal fluid pressure was effected, which lasted for two and one-half hours, and there was no secondary rise in pressure.

Another group of 10 patients, each with an operative cranial defect, was studied. Two of these were given dextrose. In 1 patient the cerebrospinal fluid pressure was reduced for one hour, followed by a return to the original level, while in the other a similar reduction was followed by a marked secondary rise in pressure. Sorbitol was administered to 2 patients. In 1 of these patients a reduction in pressure was sustained for two hours, at which time it became necessary to discontinue the experiment because of a chill. (Sorbitol when given intravenously produces chills in approximately 50 per cent of cases.) The other patient showed a reduction in cerebrospinal fluid pressure lasting approximately one hour, followed by a secondary rise in pressure. A solution of sucrose was used in 2 instances. One patient showed a reduction sustained for nearly three hours, whereas the other presented a slight reduction in cerebrospinal fluid pressure lasting for about one-half hour and followed by a secondary rise in pressure. Caffeine with sodium benzoate, in 0.5 Gm. doses given intramuscularly every hour for three hours, was used in 3 experiments in this group. No change in cerebrospinal fluid pressure was recorded in 1 instance, and in the other 2 there was a mild rise in pressure. Sodium chloride was given in the last experiment in this group. A reduction in cerebrospinal fluid pressure lasting for one hour and forty-five minutes without a secondary rise in pressure was recorded.

The last 2 of the 38 experiments were carried out on a patient with a spontaneous intracerebral hemorrhage. In the first experiment a solution of dextrose was used; this produced a prompt reduction in cerebrospinal fluid pressure, lasting for one hour only, and was followed by a marked secondary rise in pressure. In the other sucrose was used, and there was recorded a reduction in pressure lasting for one hour and fifteen minutes, without a secondary rise in pressure.

The observations made in this group of experiments on human subjects indicate that the physiologic action of the substances commonly employed for the reduction of intracranial tension cannot be predicted. Beneficial effects are therefore not to be expected in every instance in which these dehydrating agents are employed as therapeutic measures for the reduction of intracranial tension.

DISCUSSION

DR. S. BERNARD WORTIS: Dr. Browder has brought to attention an important group of observations. There is no doubt that the original studies made with dehydrating hypertonic substances did not proceed over a sufficiently long period to show the effects of secondary rises of intracranial cerebrospinal fluid pressure. Injection of hypertonic solutions of dextrose or sodium chloride into a vein raises the osmotic pressure of the blood. Dextrose and sodium chloride are both diffusible. They leave the blood stream and pass partly into the tissues, including the brain. If fluid is then taken by mouth or removed from other organs of the body, the increased sodium chloride or dextrose content of the neural tissue attracts such fluid and thereby causes a secondary rise in the spinal fluid pressure. The intravenous method of administering sucrose seems to be more efficacious in reducing intracranial cerebrospinal fluid pressure because this medicament has the advantage of leaving the blood stream, and perhaps is not as diffusible as the other substances.

A method was devised by Strecker, Mudd, Bond, Wright and Hughes (Hughes, Joseph; Mudd, Stuart, and Strecker, Edward A.: Reduction of Cerebrospinal Fluid Pressure by Concentrated Solutions of Human Lyophile Serum, ARCH. NEUROL. & PSYCHIAT. **39**:1277 [June] 1938. Wright, David; Bond, Douglas, and Hughes, Joseph: Reduction of Cerebrospinal Fluid Pressure by Concentrated Lyophile Serum: Further Observations, *ibid.* **39**:1288 [June] 1938), of Philadelphia, in which they used concentrated blood serum, injected intravenously, thereby raising the osmotic pressure of the blood. Such a method has been reported to give effective results, but confirmatory observations are required.

It is wise to remember that many procedures can change intracranial pressure under normal conditions. Many years ago, Dr. Stevenson, Dr. Christiansen and I (Some Experiments on Sleep, *A. Research Nerv. & Ment. Dis., Proc.* **8**:130, 1929), working at Bellevue Hospital, found that the intracranial pressure can be changed by many means. Simple coughing, changes in posture, certain lesions of the brain, trauma to the head, changes in respiratory rate and the effects of certain drugs can increase or diminish intracranial pressure. Part of the work with caffeine, injected hypodermically, showed a primary reduction of cerebrospinal fluid pressure, which was confirmed two years later by Dr. P. G. Denker by means of manometric thecal punctures. However, Dr. Browder is correct in emphasizing that one cannot always depend on the beneficent effect of these substances because one deals with a variety of pathologic and pathophysiologic entities when one speaks of tumor or trauma of the brain. Additional correlation of spinal fluid findings and pathophysiologic conditions would be valuable in an evaluation of the effectiveness of dehydration therapy. Also, it should be emphasized that any method which attempts to reduce the pressure in the skull, if it is to be at all effective, must reduce the pressure over a long period. Therefore it may be necessary to administer repeated doses of effective drugs, with suitable time spacing. No one perfect substance of this kind is available at present. It may be that hypertonic solution of dextrose, given intravenously, exerts part of its helpful effect by making more of this necessary brain fuel (dextrose) available to the disturbed brain cells. I believe that one of the most valuable advances in the reduction of intracranial pressure will come from a method which combines a substance like sucrose (which is readily excreted and less diffusible into the brain) with a medicament which will increase the blood protein, thereby producing a double action for reducing increased intracranial pressure.

Moreover, one sees remarkable clinical improvements with each of these spinal fluid pressure–reducing substances; perhaps if the required effect is not secured with one substance it would be wise to change to another. My associates and I have tried sorbitol at the Bellevue Hospital and found that it reduces pressure only for about twenty or thirty minutes and that an hour or an hour and a half later the intracranial pressure is greater than before we started to administer this substance.

DR. GEORGE H. HYSLOP: Will Dr. Browder please say whether in patients who for some reason have an increased intracranial pressure some of the clinical harm associated with the pressure arises from the interstitial solutes which are irritating, and whether the apparent benefits from such procedures arise from the removal or absorption of these interstitial solutes into the blood stream by osmosis? All know of the purely dehydrating factor in reducing pressure associated with acute or subacute intracranial inflammatory processes, and even neoplastic lesions.

The second question is: Has Dr. Browder any remarks about the prevalent tendency of physicians to pile speculation on speculation in cases in which there has been intracranial trauma and to hypothesize, without any clinical evidence, that there is persistent interstitial fluid or intracranial hypertension and that, furthermore, the introduction of a hypertonic solution by vein will do good? The third speculation, without any regard to the physiologic action, is whether repeated doses of 20 cc. of 50 per cent solutions by vein, two or three times a week, do any good.

DR. ABRAM BLAU: A few years ago I did a number of similar experiments at the Mount Sinai Hospital. However, in only a few instances were the patients suffering from tumor of the brain with increased cerebrospinal fluid pressure; most had other diseases of the central nervous system in which the spinal fluid pressure approximated the normal. The results of 51 observations were published (Relative Values of Caffeine and Hypertonic Dextrose and Saline Solutions in Reducing Cerebrospinal Fluid Pressure, *Arch. Int. Med.* **57**:749 [April] 1936).

Fifty cubic centimeters of 50 per cent solution of dextrose, 100 cc. of 50 per cent solution of dextrose, 50 cc. of 15 per cent saline solution, 50 cc. of 30 per cent saline solution and caffeine, 5 grains (0.3 Gm.), were administered, with observations of their effects on the spinal fluid pressure. The results were somewhat different from those of Dr. Browder, and one reason may be that most of my patients did not have cranial defects and had not had severe trauma to the head. It is interesting that the intravenous injection of 50 cc. of 50 per cent solution of dextrose produced little noticeable effect, despite the fact that this is the common procedure in neurologic practice; in only 2 cases was there a slight lowering of pressure; in 3 cases there was a definite slight rise. With 100 cc. of 50 per cent solution of dextrose injected intravenously a temporary fall occurred in only 5 cases; in 7, including 1 case of tumor of the brain, there was no appreciable change, and in 1 case a definite rise in pressure occurred. On the other hand, 15 per cent saline solution given intravenously caused a definite drop in pressure, comparable to that obtained with 100 cc. of 50 per cent solution of dextrose, while with 30 per cent saline solution the lowering of spinal fluid pressure continued effective for longer than the time of the observations, which was usually about an hour and a half. With caffeine injected intravenously, which was used more or less as a control because of the work which had already been done by Dr. Denker (The Effect of Caffeine on the Cerebrospinal Fluid Pressure, *Am. J. M. Sc.* **181**:675 [May] 1931), the effect was similar to that obtained by Dr. Denker in that the pressure dropped immediately, remained depressed for about half an hour and then returned gradually to normal without a subsequent rise in pressure.

I also noted the interesting incidental observation which Dr. Browder reports, namely, that in cases of markedly increased intracranial pressure there were marked variations in pressure over short periods and that these fluctuations of pressure were most marked in cases of cerebellar tumor. Furthermore, when the pressure is decreased by any of the solutions the extent of the variations is diminished, and the cerebrospinal fluid pressure becomes more stable.

DR. JOSEPH E. J. KING: I wish to compliment Dr. Browder on the presentation of his work and the characteristic common sense manner in which he speaks of these solutions, about which so much has been heard and so little seems

to be known. I wish to ask him if he believes in the removal of spinal fluid by lumbar puncture in cases of trauma to the brain. When does he do it in relation to the intravenous injection, and which one of the solutions does he prefer?

I have noticed, without any data to support me, that in cases of infection, especially abscesses of the brain, dehydration of the brain with the use of a solution of dextrose or sucrose takes place at a greater rate and is sustained longer than in cases of any other condition, either trauma or tumor. In a case of Dr. Friedman at the Bellevue Hospital in which a diagnosis of abscess of the right frontal lobe had been made, I remember that when I saw the patient he was chatting with his wife about family affairs. He not only did not seem to have an abscess of the brain but did not even appear to be ill. I was told that he had been given hypertonic solution of dextrose, which brought him out of a semicomatose condition. I advised that the solution be withheld for twenty-four hours. At the end of this period he was again semicomatose and showed a picture typical of an abscess of the right frontal lobe.

Dr. Lawrence S. Kubie: This topic is so important and at the same time, as Dr. Wortis pointed out, has so many pitfalls that it seems worth while to add a few more difficulties and precautions to those already pointed out. It should not surprise any one that the results vary greatly from case to case, even with the same solution. If one wishes really to standardize the procedure with these solutions, many variables must be controlled. 1. One must work with equimolecular solutions of equal osmotic action—that is, the dispersion constants must be known. 2. The solutions must be injected in an amount in keeping with the body bulk of the patient, exactly as one does in a determination of the basal metabolism. Therefore, the body surface must be taken into consideration. To give a certain amount of a solution to one person and the same amount to another of a different bulk is obviously not applying the same procedure. To have comparable results one must inject (*a*) equimolecular solutions (*b*) at a given volume per surface area per minute (*c*) to a given total amount per surface area. 3. In addition to this, one must consider the previous state of hydration of the subject. This is difficult to control even in the laboratory, with experimental animals. It is even more difficult to control in normal persons, and it is extremely difficult in patients with tumors of the brain, with disturbances in fluid intake, vomiting and the like. Nevertheless, one must attempt at least to make observations on patients under controlled "basal" conditions of fluid balance if one wishes to be sure of one's ground. 4. There is also the question of the influence of variations in hydrogen ion concentration on the dispersion and diffusion of all electrolytes, on which observations should be recorded at the time the experiment is undertaken—not only at the beginning of but throughout the experiment. That is, p_H readings should precede and accompany the injections. 5. The p_H will be influenced also by both the rate and the depth of respiration through the blowing off of carbon dioxide. If one patient is overventilating during the injection and another is breathing slowly or underventilating, a different physiochemical situation exists, and it would be naive in such cases to expect the same effects, even from identical injections. Therefore the respiratory or the carbon dioxide–combining power should be recorded. 6. Patients are known to vary in the speed with which they oxidize and excrete the sugars. This is interesting, particularly with regard to the injection of solutions of carbohydrates. Therefore, as a guide to this variable factor, the carbohydrate tolerance reactions of each patient should be known if one wishes to compare the osmotic actions of a group of carbohydrates on intracranial pressure. Obviously, the first thing one must know is how long a given sugar continues to circulate and at what concentrations. If one person burns it twice as fast as another, one would expect only half the osmotic influence. 7. Another simple and practical point which should be borne in mind is that the intracranial pressure, as measured by a needle leading to a manometer, is not identical with hydration or dehydration within the cranial cavity. The volumes

of intracranial blood and of cerebrospinal fluid are mutually compensatory. A rising venous pressure may actually mask a marked decrease in volume of cerebrospinal fluid if the algebraic sum of the two is measured merely by recording the intracranial pressure. Therefore, one may be securing a beneficial therapeutic effect, i. e., dehydration of pathologic tissue, even though that therapeutic effect may not manifest itself by a decrease in intracranial pressure because of the fact that the procedure may at the same time raise the venous pressure and increase the total volume of intracranial blood.

DR. S. BERNARD WORTIS: One does see clinical improvement following administration of each of the substances reported. Such an effect may be a resultant of many factors, and I am sure Dr. Browder will agree that it is not due alone to the reduction in intracranial pressure. For instance, if a comatose person is given an intravenous injection of dextrose it may bring him out of coma without changes in the cerebrospinal fluid pressure. Part of the benefit may be due to the fact that the brain is given more fuel (i. e., dextrose), and may thus be a specific nutritional effect.

DR. JEFFERSON BROWDER: This preliminary report was presented as a series of observations, no attempt being made to draw conclusions. The reduction in cerebrospinal fluid pressure, as measured through a spinal needle in the lumbar thecal sac, does not necessarily indicate that the intracranial pressure has been reduced to a comparable level.

Dr. Kubie's criticism of the method used in this study is entirely justified. An attempt was made to establish the same conditions in these experiments as obtains in the average case encountered in clinical practice. It would be difficult to weigh a patient in an unconscious state or to determine the degree of hydration in any given instance. It seems to me that the observations were made on a group of patients that represent a fair cross section of those encountered in hospital practice.

Dr. Hyslop raises the question of the efficacy of repeated intravenous injection of hypertonic solution in the treatment of interstitial edema associated with brain trauma. Theoretically, this method of treating patients with severe trauma is correct, but seldom does one observe any remarkable change in the patient's condition following the injection. The majority of patients with damage to the brain show no measurable increase in intracranial pressure as determined by the cerebrospinal fluid pressure in the lumbar thecal sac. According to the observations made in the experiments just presented, one should inject the hypertonic solution every hour if a sustained reduction of cerebrospinal fluid pressure is to be attained. The effectiveness of this method is indeed open to question. Nor could one expect that small doses of a dehydrating agent given at frequent intervals would result in sustained reduction in pressure.

Dr. Blau remarked that the subjects used in his observations did not have large cranial defects. In the series reported on this evening, 10 of the 38 patients had large cranial defects, and the differences in response to intravenous hypertonic solutions in this group were indicated by the charts.

Dr. King asked a question regarding the utilization of lumbar puncture in the treatment for brain trauma. By repeated lumbar puncture a small amount of subarachnoid blood may be removed. Several years ago, a series of patients with brain trauma were subjected to lumbar puncture drainage at hourly intervals. The amount of blood in the cerebral spaces of those in the group who succumbed was compared with the amount of blood in the cerebral spaces of another group of patients similarly injured but not thus treated. Little, if any, difference in the appearance of the brains in these two groups was observed. It is believed that drainage of cerebrospinal fluid by repeated lumbar puncture should not be used as a routine measure. Likewise, the intravenous injection of hypertonic solutions should not be employed as a panacea in the treatment of lesions of the brain that are thought to be associated with increased intracranial tension.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY PUTNAM, M.D., *Presiding*

Regular Meeting, Jan. 19, 1939

KORSAKOFF'S SYNDROME: CLINICAL STUDY OF THE ALCOHOLIC FORM, WITH SPECIAL REGARD TO PROGNOSIS. DR. MILTON ROSENBAUM and DR. H. H. MERRITT.

This article appeared in full in the May issue of the ARCHIVES, page 978.

RELATION OF ALCOHOLISM AND SUICIDE: A REPORT OF ONE HUNDRED AND FORTY-THREE CASES. DR. MERRILL MOORE.

This study, based on a survey of the records of 143 alcoholic suicidal patients admitted to the Boston City Hospital in recent years, is presented in an effort to provide a partial answer to the question: What relationship (if any) is there between alcoholism and suicide? All the patients were in the habit of drinking alcoholic liquors to excess and were under the influence of alcohol at the time of the suicidal attempt, or had attempted suicide shortly after drinking.

From 1915 to 1938 approximately 25,000 alcoholic patients were admitted to the Boston City Hospital. During the same period 1,195 patients were admitted after attempting suicide. Of the latter, only 143 (11 per cent) were alcoholic. Of the total number of alcoholic patients admitted to the Boston City Hospital, those who have attempted suicide constitute an extremely small fraction. If it is true, as some writers theorize, that alcoholism and suicide represent varying forms of a self-destructive drive, one may wonder why they so seldom coincide. Though alcoholism and suicide may be only symptoms of a more fundamental personality disorder, it is clinically convenient to treat each manifestation and their concurrence as a syndrome.

In the group of 143 patients there were 98 men and 45 women. Among suicidal patients from the general hospital group, women outnumbered men in the proportion of 6:5. Among all alcoholic patients admitted there were five times as many men as women.

The greatest number of suicidal attempts among alcoholic patients occurred between the ages of 30 and 40 for both men and women, whereas among non-alcoholic suicidal patients the peak was between the ages of 26 and 30 for men and 21 and 25 for women.

Although in the 143 cases the details varied considerably, there appeared constantly conditions of maladjustment—social, occupational, marital or economic. The histories obtained constantly stressed breakdown of the patient's personal adjustments and the development of symptomatic drinking (often in the pattern of addiction) and episodic emotional crises, often preceded by depression and bewilderment. Since the same general pattern of breakdown can, and often does, occur in forms other than suicide, it is interesting that so few (only 4 patients) in this series were considered sufficiently ill mentally to be committed as psychotic, although some of the 139 patients may have been temporarily irresponsible, owing to the effects of alcohol. When the patients became sober and recovered, they were for the most part embarrassed and discouraged, though still obviously confronted and disturbed by various psychologic and social difficulties.

The patients admitted to the Boston City Hospital are for the most part those who cannot afford private care. Nearly half of all admissions to the hospitals in recent years have been persons who were receiving financial aid in one form or another. Of the rest in the upper bracket, a small number have an annual income of from $1,000 to $1,500, or above. In the group considered in this study, by far the greatest number were unemployed or the employment was unknown. Few skilled workers were included. This was due partly to the social group from which the hospital draws its patients and partly to the personality difficulties of

this group of patients. The pressure produced by the financial problem often appears to be a major factor in promoting a suicidal attempt. Few of the patients have shown much interest in taking advantage of the help toward adjustment offered by the social service department of the hospital.

Of all the information obtained about suicidal patients, that concerning motivation is the most meager and unreliable. In this series, 108 of 143 patients offered no reason for the attempt, probably in most cases because they were not asked for it. The reasons stated by 20 men and 7 women were simple and inconclusive, owing to the patients' failure to understand their motivations and to the lack of adequate data from which conclusions could be drawn. The reasons stated were, in broad terms: occupational maladjustment, domestic friction, drunkenness and loneliness, with resultant frustration, deprivation and anxiety. From the information obtained, it appears that the depressive and reactive depressive group of patients understand themselves best. The compulsive and hysterical patients understand themselves less well, and the schizoid and epileptoid personalities understand themselves least of all. The same degree of understanding holds true for the observer of these patients.

More attempts at suicide occurred in June than in any other month; fewest in February. Most attempts were made on Sunday and fewest on Friday.

Poison by mouth was by far the most frequent method of attempting suicide in this group of patients, both men and women; 58 per cent of the entire group used this method. Though a wide variety of poisons were taken by mouth, iodine was by far the most common among alcoholic patients, as among those of all other groups. The ineffectiveness of iodine as a suicidal agent is probably not realized by the majority of those who attempt suicide. It is natural that most of the poisons used by the patients should have been substances that are common in the home and are usually marked "poison." The inhalation of illuminating gas ranked second among both men and women, being the method used by 11 per cent of the patients. Other less frequently used methods were slashing, jumping from high places, hanging, immersion and firearms. Two men attempted suicide by combined methods. One patient cut his wrist and turned on the gas and another cut his throat and attempted to drown himself. No woman patient attempted suicide by combined methods. No patient in this series attempted suicide by drinking alcohol alone (as a poison). Poison by mouth was the method used by 5 of the 7 patients who were successful in the suicidal attempt.

Ninety-five per cent of the patients were unsuccessful in the suicidal attempt; 89 patients (60 men and 29 women) were discharged as relieved after symptomatic treatment and a brief stay in the hospital. Twenty-five (16 men and 9 women) were discharged, against advice, before studies and treatment were completed. Five patients, all men, were transferred to other services or to the outpatient department for further treatment. Four men were considered sufficiently psychotic to require transfer to a hospital for mental disease after emergency treatment. Only 7 (5 per cent) of the 143 alcoholic suicidal patients died in the hospital as a result of the suicidal attempts. During the same period, 11 per cent of the total number of all suicidal patients died as a result of the suicidal attempts. From this it may be inferred either that alcoholic patients are less successful as a group than suicidal patients in general or that alcoholism "protects" suicidal patients from success.

It is not easy to explain why 95 per cent of the patients in this series were unsuccessful in the attempt at suicide. It is rarely possible to state whether an attempted suicide is a gesture or is bona fide. The failures were due chiefly to the ingestion of essentially nonpoisonous substances, sublethal doses when poisons were taken by mouth, quick and effective interference by relatives and friends after the attempt had been made and adequate and prompt medical and surgical treatment. An important additional factor was the alcohol itself, which in many instances appeared to derange, inhibit or render generally less efficient the technic and planning used in carrying out the suicidal attempt. The records in these 143 cases, incomplete as they often were, gave strong evidence on the last point.

THE NEUROLOGIC ASPECTS OF ALCOHOLISM. DR. LEO ALEXANDER.

The pathogenic mechanism by which the clinical manifestations of chronic damage to the nervous system by alcoholism (the alcoholic psychoses, Wernicke's disease and alcoholic polyneuronitis) come about has recently been subjected to much research and discussion. The general trend of interpretation is away from the older assumption of direct toxic action on nerve tissue by alcohol and more in favor of a vitamin deficiency, due to some of the metabolic (more specifically, avitaminotic) disturbances inaugurated by the chronic ingestion of alcohol. This alcoholic avitaminosis is due to three factors: (1) neglect of proper diet by persons chronically addicted to alcohol; (2) incomplete absorption of vitamins if taken, owing to gastritis and intestinal changes produced by alcoholism; (3) increased vitamin requirement due to the high caloric value of alcohol. The third factor may even make a normal, balanced diet inadequate for the alcoholic person, even in the presence of normal resorptive functions. Proof of the avitaminotic causation of the clinical syndromes of alcoholic damage to the nerovus system in man, however, has been definitely established only for polyneuritis (Shattuck, Meyer, Minot, Strauss and Cobb, Cobb and Coggeshall). There is much suggestive evidence that Korsakoff's psychosis may be due essentially to deficiency factors, especially if complicated by pellagrous lesions or by scurvy. This suggestive evidence receives further support from the fact that Korsakoff's syndrome may develop in deficiency states due to gastrointestinal disease and other systemic disturbances without the presence of alcoholism (Alexander and Wu). However, much less clear is the situation in delirium tremens which has not yet been found fully duplicated in any toxic or metabolic disease other than chronic alcoholism. Though certain acute hallucinatory states occurring in other toxic and febrile conditions (such as cocainism, morphine poisoning and delirium with puerperal fever) may occasionally be reminiscent of delirium tremens, there is sufficient clinical dissimilarity to allow differential diagnosis easily to be made, even without a knowledge of the history. These uncertainties, however, should not inhibit one from searching further for the possible avitaminotic factors, even in such a specific alcoholic disturbance as delirium tremens, because specific syndromes may be brought about by imbalance in the degree of deficiency of the various vitamins rather than by the presence or absence of any one vitamin. Such dynamic and possible quantitative relations are suggested by the recent experimental work of Alexander, Myerson and Pijoan. This leads to the field of pathology in which, much better than in the clinical field, one is able to show that all the pathologic changes in the nervous system of persons suffering from chronic alcoholism can be reproduced by disturbances of the vitamin metabolism.

Acute Alcoholism.—I shall limit the discussion of this disorder to cases in which the cause of death is directly and exclusively related to alcoholism. Ingestion of alcohol causes rapid dilatation of the vascular bed, including that of the brain. This, in fact, is the basis of one of the therapeutic uses of alcohol, namely, as an efficient vasodilator. If taken in excess, the vasodilatation may become extreme and lead to stasis, peristatic hemorrhages and serous transudation. Accordingly, the pathologic changes in the brain tissue in fatal acute alcoholism are hyperemia, especially of the cortical gray matter, sometimes associated with edema and flattening of the convolutions. In patients who survive for more than one day, slight perivascular histiocytic infiltrations may be seen, especially along the small and middle-sized precapillary blood vessels of the medulla oblongata. The changes are always slight, however, and may easily escape attention. Furthermore, these changes are not specific for death from acute alcoholic intoxication, but are also observed in other types of poisoning. Therefore, the best proof of the cause of death in this condition is the chemical analysis of the brain tissue for alcoholic content.

Chronic Alcoholism: Nature and Pathogenesis of the Resulting Damage to the Nervous System.—The cause of death in patients suffering from chronic alcoholism is related to their alcoholism in varying degrees. Three groups can be

distinguished. 1. A fairly large group of patients with chronic alcoholism die from trauma to the skull or to other parts of the body, due to accidents which happen during intoxication. A frequent finding in this group is subdural hemorrhage. The pathologic changes in subdural hemorrhage have been studied thoroughly by Putnam and Cushing, Leary and Merritt and Munro. The immediate cause of subdural hemorrhage in chronic alcoholism is practically always trauma. There is a possibility that chronic abuse of alcohol may lower the threshold to extravasation of blood in such a way that it may be regarded as a predisposing or contributory factor in the formation of the hemorrhage. It has been shown by Ingalls that scorbutic children are apt to suffer subdural hemorrhage on slight traumatization, and it has been demonstrated by Alexander, Pijoan, Schube and Moore that the ascorbic acid content of the blood plasma is lowered in chronic alcoholism. Occasionally, the trauma which leads to subdural hemorrhage in a chronic alcoholic patient may be so slight that it may not have been noticed or remembered by the patient and may have failed to leave a noticeable trace on the skull or scalp. Recently, a chronic alcoholic patient under my observation insisted that he had not fallen or otherwise been traumatized. Autopsy failed to disclose any bruises of the skin or of the subcutaneous tissue of the skull or injury to the bone itself, but revealed an extensive subdural hematoma of about eight days' duration (determined according to the criteria of Merritt and Munro) covering and compressing almost the entire right cerebral hemisphere. The ascorbic acid content of the blood plasma of this patient was 0.13 mg. per hundred cubic centimeters.

2. Another group of alcoholic patients die from intercurrent infections, especially pneumonia and subcutaneous abscesses. The greater death rate from pneumonia among chronic alcoholic patients as compared with persons used as controls has been emphasized by Weichselbaum, Grawitz and Leary. This may also be related to the deficiency of the alcoholic patient in vitamins, especially vitamin C, of which he is further depleted by the infectious disease. The latter fact has been demonstrated by Ingalls.

3. A third group is one in which death occurs in the course of one of the chronic diseases of the central nervous system, which develops after from five to forty-five years of chronic excessive alcoholism, namely, alcoholic psychosis and alcoholic polyneuritis. The pathologic and still more the ultimate etiologic factors in these conditions present many problems, and it is these conditions which interest me mainly. A patient suffering from one of these conditions may die suddenly or after prolonged illness with invalidism without the addition necessarily of other exogenous factors, such as trauma or infection. The pathologic manifestations in this group are of two types, which may coincide occasionally but by no means regularly. These two types of involvement are: (1) A syndrome characterized by central and peripheral neuronitis with swelling of ganglion cells, predominantly in the motor and frontal cortex and the motor horns of the spinal cord, and with degeneration of nerve fibers, predominantly of the myelin sheaths in the peripheral and central nervous system. This syndrome can be reproduced in animals by vitamin B_1 deficiency and resembles the clinical syndromes commonly found in persons suffering from beriberi or pellagra. (2) A syndrome characterized by small foci of degeneration and varicose deformity of vessels, small hemorrhages and subacute necrosis of the parenchyma, predominantly around the ventricular system, especially the basal part of the third ventricle, which was first described by Wernicke as polioencephalitis haemorrhagica superior and inferior. The vessels within these lesions, in addition, show frequently, though not always, proliferation of adventitial and endothelial elements. Although I have found this syndrome in cases of scurvy in alcoholic as well as in nonalcoholic patients, and although we (Pijoan, Schube, Moore and I) have demonstrated that the vitamin C level of the blood plasma in patients suffering from psychoses due to chronic alcoholism is consistently low, and therefore it may have been tempting to conclude that Wernicke's encephalitis haemorrhagica is a cerebral form of scurvy, Myerson, Pijoan and I have demonstrated by further experimental research that in laboratory animals (pigeons) Wernicke's disease can be reproduced by vitamin B_1

deficiency, especially if the birds are given an ample supply of one or more of the other vitamins (A, B_2, C and D). Wernicke's disease cannot be reproduced experimentally by vitamin C deficiency. Vitamin C deficiency, however, may play a role in the predisposition to subdural hematoma, which is commonly encountered in alcoholic as well as in scorbutic patients (Ingalls, Alexander, Pijoan, Schube and Moore) more commonly than could be explained by the higher incidence of trauma alone.

All the observations demonstrate that the main organic damage that alcohol inflicts on the human nervous system is due to avitaminosis rather than to primary toxic injury from alcohol itself.

DISCUSSION ON PAPERS OF DRS. ROSENBAUM AND MERRITT, MOORE AND ALEXANDER

DR. ABRAHAM MYERSON: Dr. Rosenbaum's paper adequately confirms the seriousness of Korsakoff's disease. Probably many patients who enter hospitals while not appearing very sick have conditions with a serious prognosis. Treatment, therefore, should be started immediately. I am not surprised that Dr. Moore found the suicide level so low among alcoholic persons. Apparently, suicidal feelings do not grow to serious proportions in cases of uncomplicated alcoholism. Alcohol should be given its due and is not bad treatment when one feels suicidal.

In this project for the study of alcoholism, there was perfect collaboration between the two groups of workers, at the Boston City Hospital and the Boston State Hospital. What seems to be of great importance in Dr. Alexander's presentation is the vitamin physiology. It appears that alcoholic subjects have pellagra from lack of vitamin B_2 and polyneuritis from lack of vitamin B_1. Vitamin C plays a minor role, but cannot be neglected.

The important fact about the work with pigeons is that vitamin B_1 deficiency is not only an actual deficiency but also a condition of disharmony. Whenever metabolism increases, as in pregnancy and infection the body needs increased vitamin B_1. In alcoholism, ingestion of vitamin B_1 is diminished in proportion to that of the other vitamins. This may be called a dynamic deficiency, and it is an important factor. Another point that has been brought out by these experiments is the role of the minerals. They act as essential catalysts, and the fact that the minerals were not greatly reduced allows for recovery of the cells. It is probable that the relation of vitamins to minerals needs reemphasis.

DR. A. WARREN STEARNS: It is a long time since I studied either alcoholism or suicide. It is evident that many data can be secured from the clinical material in general hospitals. There has been a tendency to overlook this. I recall frequently seeing cases of Korsakoff's syndrome at the Boston City Hospital. Since the prognosis had not seemed poor at the general hospital, I was surprised on going to the Danvers State Hospital at what a deadly disease it appeared to be.

Concerning Dr. Moore's paper: It is interesting to see the change in the ratio of the sexes among suicidal patients. A few years ago the ratio was 5:1 in favor of the men. The incidence among emancipated women has gradually risen. However, the rate among women is much greater in eastern countries, Japan and India, for instance, indicating that it may not be a sexual matter but may to some extent be due to social custom.

DR. ROBERT FLEMING: In 1934, Dr. Cobb and his associates published a paper on the relation between deficiency and peripheral neuritis. At that time a great deal of interest was shown in the clinical relation between vitamin deficiency and Korsakoff's syndrome, and many patients with Korsakoff's disease of long standing were given a high vitamin diet. Nothing happened. It would be convincing and worth while to have a series of observations in these cases before and after this treatment, that is, before 1934 and after 1938.

Will Dr. Alexander say how the ingestion of alcohol operates to cause vitamin B_1 deficiency?

DR. H. B. GRAY: I have had experience with alcoholic patients and have found that attempted suicides have been rare and that the histories are indefinite.

I do not pay much attention to the history when it speaks of suicide. Attempted suicides are rare, something like 1 in 4,000 or 5,000.

Dr. Tracy J. Putnam: Can Dr. Rosenbaum say what is the dead line beyond which it is useless to give vitamin B? It is obvious that such a dead line must exist. Also, I should like him to comment on the difference between giving vitamin B by mouth and by injection.

I wish to ask Dr. Alexander whether the stains for axis-cylinders would show changes corresponding to the clinical changes at a time when the myelin is not greatly disturbed.

Dr. Milton Rosenbaum: We have no data concerning the dead line in these cases, but since the most severe neuritis will recover in time vitamin therapy may be useful, even if given late in the illness. In general, after a severe neuritis has been treated actively for a month or so with vitamins other forms of therapy, such as physical exercise, are more important. This is significant. Many patients who were sent to institutions in 1936 died while there, and it was noted that they received no treatment during that year. However, in the past year or so, at the same institutions patients of the same type have received vitamins by mouth, physical therapy and other remedies, with marked lowering in the mortality rate; many patients were discharged, to return home. It seems one must keep on trying. It is also important to give vitamin B_1 to the patients immediately, no matter what the neuritic or mental condition is, in order to counteract the beriberi type of cardiac condition which may be present and usually causes the death of the patient. I think it is better to give vitamin B by injection in the acute forms, since many of the patients have acute gastritis, which will prevent absorption of vitamin B if given by mouth.

Dr. Merrill Moore: A question has been asked about delirium tremens. My colleagues and I now believe that we have a preferable method of treatment for patients with delirium tremens admitted to the Boston City Hospital. More and better nursing care and more medical attention are given. There are several rooms in which the patient may "roam" rather than be kept in restraint, as was formerly the custom. I believe that patients with delirium tremens who are kept in restraint "wear themselves out," and that the factor of exhaustion adds to their clinical difficulties.

I do not know what a surgeon would say if it were reported to him that a group of about 2,000 patients showed a decrease in the mortality rate from 55 to 25 per cent. At the Boston City Hospital for over twenty years the mortality rate among patients with delirium tremens has averaged 25 per cent! In the last eight or ten years, however, the rate has been decreasing, and it is lower today than it has ever been. This decrease, as I have explained, is probably due to improved methods of medical care and nursing, the giving up of restraint and the constant hammering of Dr. Putnam, Dr. Cobb, Dr. Foley and others on the fact that the alcoholic patient is a sick person.

It is possible that in the future, with better facilities for medical and nursing care, physical therapy and diet, the mortality rate in cases of delirium tremens can be cut down to 10 per cent, or even lower. This could come about under favorable conditions in the next few years.

I wish to go on record as stating that I believe it will never be possible to cut down the death rate from delirium tremens (once the condition occurs) below 4 or 5 per cent because of the complication of pneumonia. Even with the best serum treatment, pneumonia in alcoholic persons is a serious complication and one of the most important contributions to the high death rate.

Dr. Leo Alexander: Dr. Fleming has raised two important points. The first is the question of the immediate cause of the vitamin deficiency in chronic alcoholic patients. Vitamin deficiency in chronic alcoholism is due to three causes: (1) Chronic alcoholic patients are negligent of their diet. Almost all of them give a history of poor dietary habits. This applies to alcoholic persons in every social class. Even the chronic alcoholic patients who could afford good food will frequently eat finically, leaving out the foods which are richest in vitamins. A

chronic alcoholic patient whom I saw recently always helped himself, as a polite gesture, to all courses at his family table, but actually ate only the meat, leaving the remainder on his plate. (2) The second cause is incomplete absorption of vitamins if taken, due to gastritis and intestinal changes produced by alcoholism. (3) The third cause is the increased vitamin requirement due to the high caloric value of alcohol. This third factor might make even a normal balanced diet inadequate for the alcoholic person, even in the presence of normal resorptive functions. The minimum requirement for vitamins, especially B_1, increases in proportion to the caloric volume of metabolism.

The second point raised by Dr. Fleming is that concerning the apparent ineffectiveness of vitamin treatment in certain cases of deficiency disease due to chronic alcoholism. This point is of extreme interest at present. It brings up the importance of the mutual relationship of the various vitamins involved. In experimental studies which were reported at the 1938 meeting of the American Neurological Association (Alexander, L.; Myerson, A., and Pijoan, M.: Beriberi and Scurvy: An Experimental Study, *Tr. Am. Neurol. A.*, 1938, p. 135), it was shown that vitamin B_2, if given to excess in cases of vitamin B_1 deficiency, may aggravate the symptoms and create additional lesions of the Wernicke type which are not present if vitamin B_1 and B_2 are deficient. On the other hand, it is our clinical and experimental experience that nicotinic acid, if added to vitamin B_1 treatment, may increase the effectiveness of the latter. This relation and mutual balance of the various vitamins is a field for research and therapeutic endeavor which is just beginning. For clinical purposes, until more is known about this point, I believe that in order to secure optimal therapeutic results it is best to give excessive quantities of all deficient vitamins—in our own experience with chronic alcoholic patients, vitamins B_1, B_2, A and C. No harm can be done by overdosing, and an optimal concerted action of all these factors is made possible. It was after some hesitation and skepticism that I convinced myself of the value of this "shot gun" method of vitamin treatment in cases of alcoholic vitamin deficiency, but its practical value is obvious.

I wish to warn against the administration of vitamin B_2 without simultaneous administration of vitamin B_1, because of the detrimental effect which this had in our experiments with pigeons. It seems to me, though I cannot yet state definitely, that the intake of vitamin B_2 increases the requirement for vitamin B_1.

Dr. Putnam's remarks about the fundamental differences in the elementary mechanism of tissue change in the vitamin deficiency syndromes, on the one hand, and in other diseases, such as vascular lesions, on the other, is of extreme importance. Tissue damage due to vascular occlusion is characterized by early demineralization, while in beriberi, for instance, demineralization occurs late, if at all. This may be the basis for the reversibility of the vitamin deficiency syndromes, at least in their reasonably early stages.

News and Comment

THIRD INTERNATIONAL NEUROLOGICAL CONGRESS

In view of the doubt expressed by some Americans as to the advisability of holding the Third International Neurological Congress in Copenhagen from August 21 to 25, 1939, the American Committee has communicated with the Danish Committee, requesting an expression of opinion. The Danish Committee has replied that they believe that it is advisable to continue with the plans for the congress and that if present conditions continue the congress will be held in Copenhagen, as already determined.

Book Reviews

Analysis of Parergasia. By Gladys C. Terry and Thomas A. C. Rennie, M.D., with an introduction by Adolf Meyer, Henry Phipps Professor of Psychiatry, Johns Hopkins University. Nervous and Mental Disease Monograph Series no. 64. Price, $4. Pp. 202. New York: Nervous and Mental Disease Publishing Company, 1938.

This interesting clinical study from the material of the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, was undertaken at the suggestion of Dr. Adolf Meyer and supported in part by a grant from the Supreme Council of the Thirty-Third Degree Scottish Rite Masons of the Northern Jurisdiction, U. S. A. In the introduction Dr. Meyer discusses briefly the chaos that exists in the thinking about dementia praecox, which through Kraepelin's influence came to be looked on as a unitary process. The name dementia praecox carries with it grave prognostic implications which if not borne out by time and the fruitlessness of therapy lead to the other horn of the dilemma, viz., the unsoundness of the diagnostic impressions.

Seventy-seven patients were studied, not with the idea of demonstrating ultimate deterioration but from the standpoint of Meyer's earlier concepts (1906) of habit disorganization and deterioration as a pathologic process with varying degrees of devastation and permanency, to which adaptations of many kinds are made. Parergasia is used in preference to dementia praecox and schizophrenia, and refers to "disturbances developing in particular constitutional types and expressed in vague autistic fancy, projections, passivity, paranoid systematization, formal disorders of language and behavior, incongruity of affect, and motility disturbances." The patients studied had certain similarities in common in disorders of thought content, but showed many differences. All were under the personal observation of the authors for at least two weeks. Data regarding them were systematically gathered and are classified under such headings as: (1) basic data; (2) hereditary traits; (3) constitutional inferiorities and irregularities of development and functioning; (4) conditioning environmental influences; (5) family interdependencies and difficulties of adaptation; (6) extrafamilial personality difficulties and inadequacies thwarting satisfactions; (7) personality assets, achieved adaptations and opportunities potentially favorable to rehabilitation; (8) features of changing personality and psychotic development, and (9) outcome. Clinical description is subordinated to "the meaning of the reaction to and in the person." The following six fairly distinct varieties of reaction are differentiated and are illustrated with appropriate case histories. I. Aggressive reaction: (*A*) paranoid type, (*B*) hypochondriacal complaining. II. Conversion reaction (spiritual rebirth). III. Passivity reaction: (*A*) ritualism and passivity, (*B*) reaction with stupor. IV. Delirioid reaction. V. Affective reaction: (*A*) circular type, (*B*) poor intellectual endowment, (*C*) onset with depression or elation. VI. Defeatist reaction: (*A*) daydreaming type, (*B*) empty and vague type, (*C*) childlike, deteriorated type.

Section II, devoted to the life histories of the 77 patients, presents nothing exceptional concerning age or sex. A history of sensitiveness and dependency from an early age was common. The great majority of patients were single. They were doubtless from a somewhat higher educational and occupational level than patients in many other clinics. The writers are emphatic in stating that the backgrounds of the patients presented a high percentage of mental disorders or abnormalities: In 40 cases difficulties of a fairly serious nature occurred in one or both parents. Splendid tables give the data in detail. Physiologic disturbances were found commonly in the group, gastrointestinal dysfunction being

present in 76 per cent. In 46 cases the family settings were contributive to dependence and sensitivity.

In section III, on outcome, patients treated and followed for many years are included in the group, the shortest period of observation being two years. Thirty-four patients (44 per cent) were recovered or improved and did not need hospitalization. (From 7 patients no information was available.) None of the patients were treated by insulin or shock therapy. In analyzing the outcome, assets favorable to recovery were sought, and fourteen outstanding conditions or traits were correlated with recovery. These are: (1) no familial incidence of mental disorder or personality disturbance; (2) sympathetic and protective environmental situations offering opportunity favorable to readjustment at a lower level of usefulness or to comfortable acceptance of semi-invalidism; (3) adequate intellectual endowment; (4) history of previous capacity to socialize and to hold friends; (5) self estimation, interests, goals or pursuits within keeping of the capacity and practical opportunity; (6) record of previous scholastic or occupational achievements; (7) break in compensation (previously uninterrupted) in a setting of unusual situational dissatisfaction or strain which it is possible to modify; (8) intact medical rapport, expressions of need and desire to be helped, will to cooperate; (9) intact thinking and discriminative capacity; (10) intact personal appearance and habits; (11) no evidence of hallucinatory phenomena; (12) affective admixtures in the psychotic development; (13) insight into personality difficulties; (14) influence of temporary infectious disease or toxic process or other potentially modifiable gross physiologic disturbance. The traits numbered 2, 5, 7, 8, 9, 10, 11, 12 and 14 appear to be assets, and were found more frequently in patients who recovered or improved than in others. The writers are optimistic over the outcome in this group of patients, in whom serious deterioration had hitherto been expected.

In reviewing the study as a whole, one is impressed by the detailed analysis of clinical data. From that standpoint it is a contribution which varies greatly from preceding, more or less conventional studies of such disorders. The authors make no special claim of search for more fundamental biologic etiologic factors.

Contributions from the Brain Institute. Issues III and IV. S. A. Sarkissoff and I. N. Filimonoff, Editors. Price, including the atlas, 50 rubles. Pp. 538, with 222 figures, supplemented by an atlas with 83 pages of photomicrographs. Moscow, U. S. S. R.: State Brain Institute, 1938.

The Brain Institute of Moscow, one of the numerous institutions for scientific research in the Soviet Union, deals only with investigations pertaining to the morphology and electrophysiology of the brain of man and animals. Closely associated with the institute at Moscow is a special department of the Neuropsychiatric Institute of Kharkov devoted to similar work, while a laboratory of this department and a special clinic are engaged in anatomic studies in cases of aphasia, apraxia and agnosia. The present bulky volume comprises the third and fourth issues of contributions by members of the Brain Institute of Moscow on the histology and electrophysiology of the cerebral cortex. The studies covered the ontogenesis and phylogenesis of the cortex and the brains of anthropoid apes and terrestrial carnivora (bears, dogs, lions, tigers, wolves and other animals). In addition, the brains of embryos of from 14 to 16 weeks, of a prematurely born infant, of children and of men and women were studied. In short, various areas of the cerebral cortex were studied not only after but before the brain reached its full development, and especially during the intermediate phases. Each lobe has been investigated by an individual research worker, known for his contributions to special fields of neuroanatomy and neurophysiology.

Conclusions arrived at by each contributor are that during the process of ontogenesis there are many intermediary formations in the cortex, that, in addition to its well established types of isocortex (possessing six layers) and allocortex

(possessing less than six layers), there exists a third type, called by Filimonoff "mesocortex." The mesocortex comprises the intermediary types which are so common and which in their structure resemble both isocortex and allocortex. The structure of separate areas of the cortex changes gradually, but steadily. For instance, the histologic features of the temporal lobe differ from those of the neighboring fields by a series of intermediary formations, though there are areas in which the changes are as abrupt as if delimited by a straight line. In short, some formations are typical in structure; others possess transitional features. Even an individual field by no means represents a uniform structure, the variety of the changes being great. The observations have been recorded in great detail. For instance, the description of what Filimonoff called "Ammon's zone" covers 73 pages, with 23 pictures in the text, in addition to 120 photomicrographs in the atlas.

Two contributions (by Sarkissoff and Livanoff) deal with investigations on the bioelectric currents produced by various stimulations of the brains of rats, dogs, monkeys, rabbits and other animals. These investigators found that the cortical areas differ from one another not only morphologically but neurophysiologically, exhibiting a different variety of biocurrents, and that even each cortical layer emits specific currents. Because of the close relationship existing between the morphologic and the electrophysiologic peculiarities of the cortex, it is possible, in the opinion of these investigators, to shed more light on the teaching of cerebral localization. Of other interesting conclusions, one is strongly emphasized—the absence of cortical changes caused by racial factors.

On the whole, the contributions are of great scientific interest and are highly authoritative, for they are based on studies of an enormously rich material, are excellently organized and are backed by unlimited means. Each article has a good bibliography and a generous summary, not only in Russian but also in French, German and English. The book is supplemented by a magnificent atlas, 17 by 11¾ inches (43 by 30 cm.), comprising 83 pages and 306 large photomicrographs.

Précis de neuro-psychiatrie infantile. By Gilbert Robin. Paper. Price, 60 francs. Pp. 311. Paris: Gaston Doin & Cie, 1939.

This is the first book the reviewer has seen which attempts to present a comprehensive survey of the psychiatric disorders of children. It is divided into six sections. In the first section the author presents a classification of the types of children he has observed and describes each type. He believes that the etiologic factor in some cases is a constitutional predisposition, in others an endocrine dysfunction and in others an emotional intrapsychic conflict or poor upbringing. He classifies these types as: (1) nervous children; (2) restless children; (3) children with cyclothymic reactions; (4) emotionally retarded children (the perpetual babies); (5) psychasthenic and neurasthenic children; (6) children who are pathologic liars; (7) hysterical children; (8) schizoid children; (9) paranoid children; (10) children with an epileptic personality.

In the second part Robin discusses the behavior manifestations of epilepsy and epidemic encephalitis. In the third part he describes the child with intellectual defects, including both feeblemindedness and disorders of reading and writing. In the fourth part he discusses deteriorating psychoses in children. In the fifth section he discusses the more common types of symptomatic behavior, such as speech disorders, temper tantrums, lying, truancy, stealing, feeding difficulties, enuresis and night terrors. The last section is devoted to therapeutic technics. There is a discussion of methods of reeducation for mentally defective children, of psychotherapy for behavior problems (including a description of adlerian technics and of psychoanalysis) and of institutional treatment of delinquents.

The book thus brings together under one cover the majority of the behavior problems presented by children. However, it is an outline and suffers from the usual faults of an outline. The discussions of etiology, pathology and treatment

are too abbreviated to be helpful except to the experienced child psychiatrist. The author leans too strongly to an organic and endocrine point of view in therapy. Consideration of the home situation and of parental attitudes is usually omitted.

This book should be used with caution. It is not recommended for medical students or for pediatricians. To students of child psychiatry and to practicing psychiatrists who have had little experience with children's problems it will be helpful as an introductory outline, supplemented by a bibliography which is carefully selected for its adequate presentation of pathology and treatment. As is usual with European publications, there is little reference to American authorities, who have done the major amount of research in the psychiatric disorders of childhood. The work of Orton on strephosymbolia is described briefly, and that of Alexander, Doll, Terman and Patry is mentioned.

Introduction to the Rorschach Method: A Manual of Personality Study. By Samuel J. Beck, Ph.D., with a preface by F. L. Wells. Monograph no. 1 of the American Orthopsychiatric Association. Cloth. Pp. 278, with 15 tables and 10 illustrations. Menasha, Wis.: George Banta Publishing Company, 1937.

This manual is the first monograph published by the American Orthopsychiatric Association. It provides a manual of Rorschach test procedure for use in further experimental work, the collection of comparable material and diagnostic applications. The bulk of the manual, which consists of two parts, with a preface by F. L. Wells, contains experimental records of 59 cases, descriptive of ten groups. The response records, scored and interpreted, have been taken from healthy adults of superior intelligence; from feebleminded persons; from patients with depressed states, hypomanic conditions, schizophrenia, neuroses and conduct disorders, and from problem children. Validation of records has been made by case history and clinical check-up. No attempt is made to treat the material statistically for the purpose of establishing quantitative measures of validity and reliability. The second part of the manual presents scoring technics, norms and suggested psychologic processes that the test results indicate. The norms are held to be tentative and provisional "in the extreme."

The Rorschach procedure, Beck believes, is not a test, and its use is not a technic. The methods of interpretation are intuitive to a considerable extent. Intuition, however, must be verified by experience and supplemented by analysis and inference. The customary statistical technic can be utilized to form a firm basis for the intuitive comprehension of the organization of the personality as a whole. The Rorschach procedure has long been attacked as lacking in properly established norms and standards of interpretation. Beck's manual is an attempt in the direction of remedying these deficiencies. It is hoped that, later, indexes of validity and reliability and norms with measures of dispersion will also be provided.

The manual represents careful work. The experimental records are models of skill and erudition. The Rorschach procedure itself is being widely used and compared with life histories and case records, with apparent advantage. The psychiatrist will find the manual useful in supplementing his diagnosis. The psychologist who accepts intuition as a valuable aid in the comprehension of the total personality will find a wealth of provocative relationships suggested for further investigation.

Essai de traitement de la migraine et de l'epilepsie les solutions, hypertoniques: Etude clinique et experimentale. By J. F. Buvat. Price, $2.00. Pp. 155. Paris: E. Le François, 1938.

In addition to the regular administration of phenobarbital and potassium borotartrate, 35 epileptic patients received treatment three times a week with the following: an intravenous injection of 20 cc. of a 10 per cent solution of sodium

chloride and 10 per cent sodium bromide and drop enemas consisting of 15 per cent magnesium sulfate and 10 per cent sodium bromide. Twelve patients with status epilepticus were given from 20 to 40 cc. of the hypertonic solution. Approximately two thirds of the patients showed some improvement either in seizures or in behavior. Seven patients having an attack of migraine received intravenous injections. All were relieved of the existing headache, and some subsequently had headaches more rarely. Scattered observations were also made of the effect of the injection on the pressure of the cerebrospinal fluid, the p_H of the urine and the concentration of the blood. Various theories and observations dealing with the cause of the attacks of epilepsy and of migraine are named and discussed superficially. In spite of the absence of a consistent fall of cerebrospinal fluid pressure following the hypertonic injections (a failure of lumbar pressure to follow intraventricular pressure is postulated), the author believes that the beneficial effect of the hypertonic injections in treatment of epilepsy and migraine may be due to dehydration of the brain. He seems to disregard the direct sedative action of the bromide.

The Treasury of Human Inheritance. Vol. IV: Nervous Diseases and Muscular Dystrophies. Pt. 1: Huntington's Chorea. R. A. Fisher, F.R.S., editor. Edited by Julia Bell, M.A., M.R.C.P. Paper. Price, 10 s. Pp. 67, with 12 illustrations. London: Cambridge University Press, 1934.

This volume is concerned primarily with the hereditary and genealogic aspects of Huntington's chorea, and the bulk of the material is a detailed summary of most of the case histories and pedigree charts contained in the literature up until 1932. The section dealing with incidence, age, sex, duration and associated disorders is derived apparently from the mass of cases reported in the literature, but there is no statement to indicate the specific sources of each statistical summary. Studies, particularly that of Vessie in 1932, have indicated that the disease was introduced into the United States from England, and Bell cites attempts to verify or disprove this assumption. One obtains the impression, however, that Huntington's chorea is exceedingly rare in England.

An interesting disclosure, to the reviewer at least, is the comparatively large number of cases of the disease in which the onset of symptoms occurred during the first two decades of life. The author has succeeded in presenting a complete summary of available genealogic information with regard to a disease which is said to be the "most hereditary" of hereditary disorders.

Recherches sur l'embryologie du système nerveux central. By André Barbé. Preface by A. Souques. Price, 250 francs. Pp. 340, with 275 figures. Paris: Masson & Cie, 1938.

The author has undertaken a systematic study of the development of the human central nervous system from both the macroscopic and the microscopic standpoint. He has prepared sections of the fetal brain by most of the principal staining methods and reproduces unretouched photographs of these sections. The earliest stage is represented by one 14 mm. embryo, and the greater part of the book deals with specimens the gestation age of which was more than four months. This much can be said of Dr. Barbé's investigation: He has been honest in disclosing the imperfection of his material. Most of the fetuses, one may judge from the illustrations, either were poorly preserved or were abnormal. Many of the photomicrographs of sections show so little normal embryonic development as to be of no value whatever. Although there exist in other languages a number of excellent works on development of the nervous system, the author either is unfamiliar with or has entirely ignored them, for his bibliography is limited to seventeen titles, all of which are textbooks or monographs published in French.